Annex

Nicotine in Cigarettes and Smokeless Tobacco Is a Drug and These Products Are Nicotine Delivery Devices Under the Federal Food, Drug, and Cosmetic Act: Jurisdictional Determination

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
U.S. Food and Drug Administration

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EXECUTIVE SUMMARY

This document explains the basis for the Food and Drug Administration's assertion of jurisdiction over cigarettes and smokeless tobacco under the Federal Food, Drug, and Cosmetic Act (the Act). FDA regulates a diverse range of products under the Act, including foods, drugs, medical devices, and cosmetics. The distinguishing feature that characterizes these products is their intimate and potentially harmful relationship with the human body. The products that FDA regulates include those that are ingested, inhaled, implanted, or otherwise used in close contact with the human body.

Cigarettes, which deliver a pharmacologically active dose of nicotine to the body through inhalation, and smokeless tobacco, which delivers a pharmacologically active dose of nicotine to the body through buccal absorption, share this distinguishing feature. Like the products that FDA traditionally regulates, cigarettes and smokeless tobacco are inhaled or placed within the human body; like many of these products, they deliver a pharmacologically active substance to the bloodstream; and like these products, they have potentially dangerous effects. Indeed, no products cause more death and disease than cigarettes and smokeless tobacco.

FDA is asserting jurisdiction over cigarettes and smokeless tobacco under the drug and device provisions of the Act. Specifically, FDA has concluded that cigarettes and smokeless tobacco are combination products consisting of nicotine, a drug that causes addiction and other significant pharmacological effects on the human body, and device components that deliver nicotine to the body. FDA last considered whether cigarettes were drugs or devices in the late 1970's. *See Action on Smoking and Health v. Harris.*

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655 F.2d 236 (D.C. Cir. 1980). Since that time, substantial new evidence has become available to FDA. This evidence includes the emergence of a scientific consensus that cigarettes and smokeless tobacco cause addiction to nicotine and the disclosure of thousands of pages of internal tobacco company documents detailing that these products are intended by the manufacturers to affect the structure and function of the human body. This new evidence justifies the Agency's determination that cigarettes and smokeless tobacco are delivery systems for the drug nicotine.

Under the Act, a product is a drug or device if it is an article (other than food) "intended to affect the structure or any function of the body." Sections 201(g)(1)(C), 201(h)(3). The statutory definition is "intended to define 'drug' far more broadly than does the medical profession." *United States v. An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 793, 798 (1969). The legal question of whether cigarettes and smokeless tobacco are subject to FDA jurisdiction is one that "FDA has jurisdiction to decide with administrative finality." *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 653 (1973).

After intensive investigation and careful consideration of the public comments, FDA concludes that cigarettes and smokeless tobacco meet the statutory definition of a drug and a device. This conclusion is based on two determinations: (1) nicotine in cigarettes and smokeless tobacco does "affect the structure or any function of the body," and (2) these effects on the structure and function of the body are "intended" by the manufacturers.

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The Agency's determination that nicotine in cigarettes and smokeless tobacco does "affect the structure or any function of the body" is based on three central findings:

1. Nicotine in cigarettes and smokeless tobacco causes and sustains addiction.

2. Nicotine in cigarettes and smokeless tobacco causes other psychoactive (mood-altering) effects, including tranquilization and stimulation.

3. Nicotine in cigarettes and smokeless tobacco controls weight.

The Agency's determination that the manufacturers of cigarettes and smokeless tobacco "intend" these effects is based on five central findings:

1. The addictive and other pharmacological effects of nicotine are so widely known and accepted that it is foreseeable to a reasonable manufacturer that cigarettes and smokeless tobacco will cause addiction to nicotine and other significant pharmacological effects and will be used by consumers for pharmacological purposes, including sustaining their addiction to nicotine.

2. Consumers use cigarettes and smokeless tobacco predominantly for pharmacological purposes, including sustaining their addiction to nicotine, mood alteration, and weight loss.

3. Manufacturers of cigarettes and smokeless tobacco know that nicotine in their products causes pharmacological effects in consumers, including addiction to nicotine and mood alteration, and that consumers use their products primarily to obtain the pharmacological effects of nicotine.

4. Manufacturers of cigarettes and smokeless tobacco design their products to provide consumers with a pharmacologically active dose of nicotine.

5. An inevitable consequence of the design of cigarettes and smokeless tobacco to provide consumers with a pharmacologically active dose of nicotine is to keep

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consumers using cigarettes and smokeless tobacco by sustaining their addiction to nicotine.

This document is divided into six sections. Section I describes the evidence and legal basis supporting the Agency's finding that cigarettes and smokeless tobacco "affect the structure or any function of the body." Section II describes the evidence and legal basis supporting the Agency's finding that the manufacturers "intend" these effects on the structure and function of the body. Section III explains the Agency's conclusion that cigarettes and smokeless tobacco are combination products that contain a "drug" and a "device." Section IV explains why the Agency's decision to assert jurisdiction over cigarettes and smokeless tobacco is justified by the new evidence now available to the Agency. Section V demonstrates that Congress has not precluded or preempted the Agency's assertion of jurisdiction over cigarettes and smokeless tobacco. Section VI addresses procedural issues relating to the Agency's assertion of jurisdiction over cigarettes and smokeless tobacco. These sections are summarized below.

1. Cigarettes and Smokeless Tobacco "Affect the Structure or any Function of the Body" Within the Meaning of the Act

The nicotine delivered by cigarettes and smokeless tobacco has significant pharmacological effects on the structure and function of the body.

First, the nicotine in cigarettes and smokeless tobacco causes and sustains addiction. Nicotine exerts psychoactive, or mood-altering, effects on the brain that motivate repeated, compulsive use of the substance. These pharmacological effects create dependence in the user. The pharmacological processes that cause this addiction to nicotine are similar to those that cause addiction to heroin and cocaine.

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Second, the nicotine in cigarettes and smokeless tobacco produces other important pharmacological effects on the central nervous system. Under some circumstances and doses, the nicotine has a sedating or tranquilizing effect on mood and brain activity. Under other circumstances and doses, the nicotine has a stimulant or arousal-inducing effect on mood and brain activity.

Third, the nicotine in cigarettes and smokeless tobacco affects body weight.

These effects on the structure and function of the body are significant and quintessentially drug-like. Moreover, these effects are the same as the effects of other drugs that FDA has traditionally regulated, including stimulants, tranquilizers, appetite suppressants, and products, such as methadone, used in the maintenance of addiction. For these reasons, the Agency finds that cigarettes and smokeless tobacco "affect the structure or any function of the body" within the meaning of the Act.

II. Cigarettes and Smokeless Tobacco Are "Intended" to Affect the Structure and Function of the Body Within the Meaning of the Act

To determine whether effects on the structure or function of the body are "intended" by the manufacturer, the Agency must objectively evaluate all the relevant evidence of intent in the record before it. "The FDA is not bound by the manufacturer's subjective claims of intent," but rather can find actual intent "on the basis of objective evidence." *National Nutritional Foods Ass'n v. Mathews*, 557 F.2d 325, 334 (2d Cir. 1977). In the case of cigarettes and smokeless tobacco, the Agency finds that three types of objective evidence provide independent bases for finding that the manufacturers intend to affect the structure and function of the body: (1) the evidence of the foreseeable pharmacological effects and uses of cigarettes and smokeless tobacco; (2) the evidence of

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Consumer use
Subsidiary

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the actual consumer use of cigarettes and smokeless tobacco for pharmacological purposes; and (3) the evidence of the statements, research, and actions of the manufacturers themselves. Considered independently or cumulatively, this evidence convincingly demonstrates that cigarettes and smokeless tobacco are intended to be used for pharmacological purposes.

A. *A Reasonable Manufacturer Would Foresee that Tobacco Products Will Cause Addiction and Other Pharmacological Effects and Will Be Used by Consumers for Pharmacological Purposes*

When Congress enacted the current definition of "drug" in 1938, it was well understood that "[t]he law presumes that every man *intends* the legitimate consequences of his own acts." *Agnew v. United States*, 165 U.S. 36, 53 (1897). Consistent with this common understanding, FDA's regulations provide that a product's intended pharmacological use may be established by evidence that the manufacturer "knows, or has knowledge of facts that would give him notice," that the product is being widely used for a pharmacological purpose, even if the product is not being promoted for this purpose. 21 CFR 201.128, 801.4. Thus, FDA may find that a manufacturer intends its product to affect the structure or function of the body when it would be foreseeable to a reasonable manufacturer that the product will (1) affect the structure or function of the body and (2) be used by a substantial proportion of consumers to obtain these effects. For example, when it is foreseeable to a reasonable manufacturer that a product will produce drug effects in consumers and be purchased by a substantial proportion of consumers for drug purposes, FDA may consider the product a "drug."

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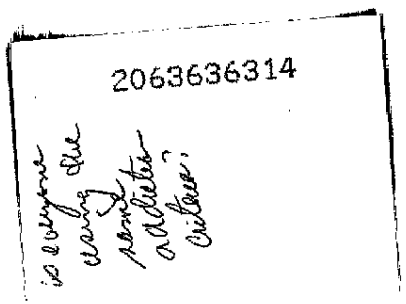

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In the case of cigarettes and smokeless tobacco, no reasonable manufacturer could fail to foresee that these products will have significant pharmacological effects on consumers and be widely used by consumers for pharmacological purposes. All major public health organizations in the United States and abroad with expertise in tobacco or drug addiction now recognize that the nicotine delivered by cigarettes and smokeless tobacco is addictive. The first major organization to do so was the American Psychiatric Association, which in 1980 defined the "tobacco dependence disorder" and the "tobacco withdrawal syndrome." Since 1980, nicotine in tobacco products has also been recognized as addictive by the U.S. Surgeon General (1986 and 1988), the American Psychological Association (1988), the Royal Society of Canada (1989), the World Health Organization (1992), the American Medical Association (1993), and the Medical Research Council in the United Kingdom (1994). Every expert medical organization that submitted comments to FDA on whether nicotine is addictive concluded that it is. The tobacco industry's public position that nicotine is not addictive is simply not credible in light of this overwhelming scientific consensus.

The scientific consensus that cigarettes and smokeless tobacco cause addiction to nicotine makes it foreseeable to a reasonable manufacturer that these products will affect the structure and function of the body. This scientific consensus also makes it foreseeable that cigarettes and smokeless tobacco will be used by a substantial proportion of consumers for a pharmacological purpose—namely, to satisfy their addiction.

It is also foreseeable that the nicotine in cigarettes and smokeless tobacco will cause, and be used for, other significant pharmacological effects. It is well established that

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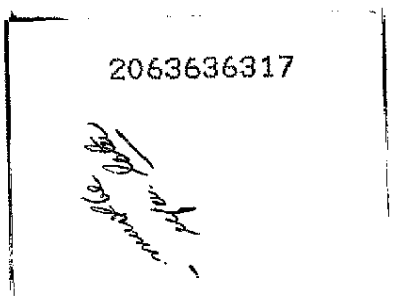

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the nicotine in cigarettes and smokeless tobacco has psychoactive or mood-altering effects in the brain. Under some circumstances, nicotine can have a sedative or tranquilizing effect on the brain; under other circumstances, nicotine can have a stimulating or arousal-inducing effect. In this regard, nicotine is similar to other addictive drugs such as opiates, which can have both stimulating and sedating effects. In addition, nicotine plays a role in weight regulation, with substantial evidence demonstrating that cigarette smoking leads to weight loss.

Because a reasonable manufacturer would foresee that cigarettes and smokeless tobacco will cause and be used for these well-established pharmacological effects in a substantial proportion of consumers, the Agency finds that these drug effects and drug uses are intended by the manufacturers.

B. Consumers Use Tobacco Products to Obtain the Pharmacological Effects of Nicotine and to Satisfy Their Addiction

A second basis for establishing that a product is intended to affect the structure or function of the body is evidence showing that consumers actually use the product for pharmacological purposes. In fact, courts have recognized that even in the absence of any other evidence of intent to affect the structure or function of the body, such an intent may be established by evidence showing that consumers use the product "predominantly" for pharmacological purposes. *ASH*, 655 F.2d at 239-240.

In the case of cigarettes and smokeless tobacco, the evidence establishes that consumers do use these products "predominantly" for pharmacological purposes. Major recent studies have concluded that 77% to 92% of smokers are addicted to nicotine in cigarettes. The U.S. Department of Health and Human Services estimates that 75% of

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young regular users of smokeless tobacco are addicted to nicotine in these products. The comments from the American Heart Association, the American Lung Association, and the American Cancer Society, whose member physicians provide health care for tobacco users in the United States, confirm that "the vast majority of people who use nicotine containing cigarettes and smokeless tobacco do so to satisfy their craving for the pharmacological effects of nicotine; that is, to satisfy their drug dependence or addiction."

In addition, a large proportion of consumers also use cigarettes and smokeless tobacco for other pharmacological purposes. A recent survey found that over 70% of young people 10 to 22 years old who are daily smokers reported that they use cigarettes for relaxation. The same survey found that over 50% of young people who are daily users of smokeless tobacco reported that they use smokeless tobacco for relaxation. Other surveys show that between one-third and one-half of young smokers report that weight control is a reason for their smoking.

This evidence that consumers actually use cigarettes and smokeless tobacco predominantly to obtain the pharmacological effects of nicotine leads FDA to find that cigarettes and smokeless tobacco are intended to affect the structure and function of the body.

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C. *The Statements, Research, and Actions of the Cigarette Manufacturers Show that the Manufacturers Intend to Affect the Structure and Function of the Body*

A third basis for establishing that a manufacturer intends to affect the structure or function of the body is evidence from the statements, research, and actions of the manufacturer that reveals that the manufacturer knows that its product will, or designs its

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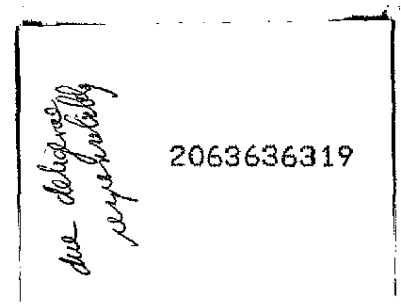

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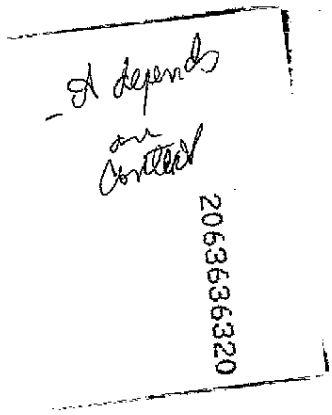

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product to affect the structure or function of the body. It is a canon of statutory construction that words used by Congress should ordinarily be interpreted in accordance with their plain meaning. The plain meaning of "intend" includes "to have in mind" or "to design" for a particular use. The *American Heritage Dictionary*, for instance, defines "intend" as: "1. To have in mind; plan. 2.a. To design for a specific purpose. b. To have in mind for a particular use." Consistent with the plain meaning of "intend," FDA may consider whether the statements, research, and actions of the manufacturer show that the manufacturer "has in mind" that its product will, or "designs" its product to, affect the structure or function of the body.

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The administrative record contains three decades of documents and other evidence from the major cigarette manufacturers. This evidence, most of which has only recently become available, establishes that the manufacturers do "have in mind" that their products will have and be used for pharmacological effects. First, the evidence shows that the cigarette manufacturers know that nicotine is a pharmacologically active drug. In internal documents, for instance, researchers for Philip Morris Inc. call nicotine "a powerful pharmacological agent with multiple sites of action" and "a physiologically active . . . substance . . . [which] alters the state of the smoker by becoming a neurotransmitter and a stimulant"; a researcher for R.J. Reynolds Tobacco Co. (RJR) calls nicotine "a potent drug with a variety of physiological effects"; and researchers for Brown & Williamson Tobacco Corp. and its parent company, BAT Industries PLC (formerly the British-American Tobacco Co.) (BATCO), call nicotine "pharmacologically active in the brain"

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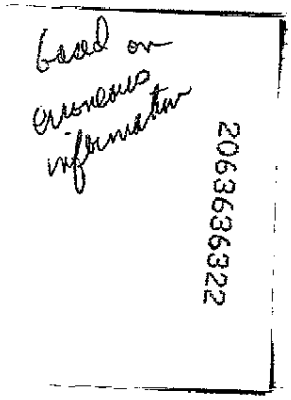

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and "an extremely biologically active compound capable of eliciting a range of pharmacological, biochemical, and physiological responses."

Second, the evidence establishes that the cigarette manufacturers have conducted extensive research to understand precisely how nicotine affects the structure and function of the body. In one year alone, Philip Morris conducted 16 different studies on the effects of nicotine, including 5 experiments to determine the pharmacological effects of nicotine on the human brain. RJR's similarly extensive research found that the nicotine in cigarettes produces measurable changes in brain wave activity, such as "a significant increase in beta2 magnitude" (an effect associated with anxiety relief) and "a significant decrease in delta magnitude" (an effect associated with improved mental condition). Through the Council for Tobacco Research, an organization formed by the major tobacco companies, the manufacturers funded dozens of sophisticated investigations concerning nicotine, including numerous studies that demonstrate nicotine's ability to alter the function of the human brain.

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Third, the evidence shows that the manufacturers know that one of the pharmacological effects of nicotine is to cause and sustain addiction. Researchers and senior officials of Brown & Williamson and BATCO expressly acknowledge this fact in their internal documents, stating that "smoking is a habit of addiction" and that "nicotine is addictive." Philip Morris scientists also know of nicotine's addiction potential. They conducted a series of nicotine "self-administration" experiments using the tests used by the National Institute on Drug Abuse to determine whether a substance has addiction potential. These studies found that rats would self-administer nicotine, which is one of the

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hallmark characteristics of an addictive drug. Moreover, through the Council for Tobacco Research, the cigarette manufacturers funded research that reported that "smoking is a form of dependence no less binding than that of other addictive drugs."

Fourth, the evidence shows that the manufacturers know that consumers smoke cigarettes primarily to obtain the pharmacological effects of nicotine. This point is repeatedly acknowledged in internal company documents. For example, researchers for Philip Morris have stated that nicotine is "the primary reason why people smoke" and that nicotine is "the physiologically active component of smoke having the greatest consequence to the consumer"; researchers for RJR have stated that "the confirmed user of tobacco is primarily seeking the physiological 'satisfaction' derived from nicotine" and that "[w]ithout any question, the desire to smoke is based upon the effect of nicotine on the body"; and BATCO's director of research has stated that "[t]he tobacco smoking habit is reinforced or dependent upon the psycho-pharmacological effects mainly of nicotine." This knowledge of the central role of nicotine in cigarette smoking was communicated to the highest levels of the companies. In 1969, for instance, Philip Morris' vice president for research and development told the Philip Morris board of directors that "the ultimate explanation for the perpetuated cigarette habit resides in the pharmacological effect of smoke upon the body of the smoker."

Fifth, the evidence shows that in their internal documents, the cigarette manufacturers expressly refer to cigarettes as devices for the delivery of nicotine. For instance, researchers for Philip Morris have described cigarettes as a "dispenser for a dose unit of nicotine" and as a "nicotine delivery device"; a senior researcher for RJR has

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described cigarettes as a "vehicle for delivering nicotine"; and researchers for BATCO have described cigarettes as the "means of providing nicotine dose in a metered fashion" and as a device that provides the smoker "very flexible control over titrating his desired dose of nicotine."

This evidence establishes that cigarettes are intended by the manufacturers to affect the structure and function of the body. It demonstrates that the manufacturers know that nicotine is pharmacologically active; that consumers smoke primarily to obtain the pharmacological effects of nicotine; and that cigarettes function as devices for the delivery of nicotine. The evidence thus shows that when the manufacturers offer cigarettes for sale, they "have in mind" that their products will be used for the particular purpose of affecting the structure and function of the body.

In addition to the evidence showing that cigarette manufacturers "have in mind" the use of cigarettes for pharmacological purposes, the record shows that the manufacturers "design" cigarettes to ensure the delivery of a pharmacologically active dose of nicotine to the smoker. The evidence in the record shows that the manufacturers have conducted extensive product research and development to find ways to maintain adequate nicotine levels in low-tar cigarettes. According to one former senior official at Philip Morris, "a key objective of the cigarette industry over the last 20-30 years" was "maintaining an acceptable and pharmacologically active nicotine level" in low-tar cigarettes. Internal industry documents in the record disclose research to determine the dose of nicotine that must be delivered to provide "pharmacological satisfaction" to the

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smoker, as well as estimates by industry scientists of the minimum and optimum doses of nicotine that cigarettes must deliver.

Among the many examples in the record of product research and development to enhance relative nicotine deliveries, Philip Morris conducted extensive research to identify "the optimal nicotine/tar ratios for cigarette acceptability of relatively low-delivery cigarettes"; RJR developed alternative tobacco products that provide a "more efficient and direct way to provide the desired nicotine dosage than the present system involving combustion of tobacco"; and Brown & Williamson investigated chemical manipulation to raise smoke pH, thereby increasing "free" nicotine delivery, and used genetic engineering to breed a high-nicotine tobacco plant called Y-1.

The record before the Agency shows that several methods of enhancing nicotine deliveries are used in the manufacture of commercial cigarettes. Tobacco blending to raise the nicotine concentration in low-tar cigarettes is common. As the vice chairman and chief operating officer of Lorillard Tobacco Co. has stated, "the lowest tar segment is composed of cigarettes utilizing a tobacco blend which is significantly higher in nicotine." Another common technique for enhancing nicotine deliveries in low-tar cigarettes is the use of filter and ventilation systems that by design remove a higher percentage of tar than nicotine. Yet a third type of nicotine manipulation is the addition of ammonia compounds that increase the delivery of "free" nicotine to smokers by raising the alkalinity or pH of tobacco smoke. These ammonia technologies are widely used within the industry.

The record establishes that an important reason why the manufacturers design cigarettes that provide pharmacologically active doses of nicotine is to satisfy the demands

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of users.. The manufacturers concede in their comments that their "intent is to design, manufacture and market . . . cigarettes to meet the preferences of adult smokers." The preferences of most smokers, however, include obtaining sufficient nicotine to sustain their addiction and to experience nicotine's mood-altering effects. What the cigarette manufacturers describe as producing cigarettes that satisfy consumer preferences is, in reality, producing cigarettes that provide the pharmacological effects of nicotine sought by consumers. The effect of maintaining a pharmacologically active dose of nicotine in cigarettes is to keep consumers smoking by sustaining their addiction.

The evidence that the manufacturers "design" cigarettes to provide a pharmacologically active dose of nicotine is further proof that the manufacturers intend cigarettes to affect the structure and function of the body. Taken together, the evidence shows that the cigarette manufacturers: (1) "have in mind" the use of cigarettes for the particular purpose of delivering the pharmacological effects of nicotine, and (2) "design" their products to provide these effects. This evidence convincingly demonstrates that the pharmacological effects of cigarettes are "intended" by the manufacturers.

D. The Statements, Research, and Actions of the Smokeless Tobacco Manufacturers Show that the Manufacturers Intend their Products to Affect the Structure and Function of the Body

The administrative record also contains evidence of the statements, research, and actions of the smokeless tobacco manufacturers. Like the evidence of the statements, research, and actions of the cigarette manufacturers, this evidence establishes that the smokeless tobacco manufacturers intend to affect the structure and function of the body.

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First, the evidence in the record shows that the smokeless tobacco manufacturers know that nicotine is a pharmacologically active drug and that consumers use smokeless tobacco to obtain the pharmacological effects of nicotine. As a senior vice president for United States Tobacco Co. (UST) stated, "virtually all tobacco usage is based upon nicotine, 'the kick,' satisfaction." Researchers affiliated with Brown & Williamson acknowledge that "nicotine . . . absorbed through . . . the lining of the nose or mouth . . . will quickly enter a direct route, in the blood, to the brain."

Second, the evidence shows that the smokeless tobacco manufacturers manipulate the nicotine delivery of their products in a manner that promotes tolerance and addiction to nicotine. This manipulation is accomplished through the use of chemicals that alter the pH of the smokeless tobacco. Moist snuff brands that are marketed as "starter" brands have a low pH and consequently deliver a low level of "free" nicotine to the user, limiting the absorption of nicotine in the mouth. The low nicotine deliveries allow the new user to develop a tolerance to nicotine without experiencing adverse reactions such as nausea and vomiting. In contrast, moist snuff brands that are marketed to experienced users have a high pH and consequently deliver a high level of "free" nicotine to the user, increasing the amount of nicotine available for absorption. The increased nicotine deliveries provide sufficient nicotine to sustain the user's addiction.

Third, the evidence shows that smokeless tobacco use and addiction to nicotine has substantially increased among teenagers since the manufacturers began to manipulate nicotine deliveries. Before the introduction of starter brands with low levels of nicotine delivery, virtually no teenagers and young adults used smokeless tobacco. After the

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smokeless tobacco manufacturers began to market low-nicotine "starter" brands in the 1970's, however, use of smokeless tobacco by teenagers rose dramatically. Use of smokeless tobacco by adolescent males aged 18 to 19, for instance, increased almost 1,500% between 1971 and 1991. Most of the regular teenage users of smokeless tobacco graduate to higher nicotine brands. An analysis by the Centers for Disease Control and Prevention found that the pattern of smokeless tobacco use by teenagers "support[s] the hypothesis that snuff users in earlier stages of tobacco use and nicotine addiction use brands with low levels of free nicotine and then 'graduate' to brands with high levels."

This evidence of: (1) knowledge of nicotine pharmacology, (2) manipulation of nicotine deliveries, and (3) graduation to higher nicotine brands among young users is a sufficient basis to establish that the smokeless tobacco manufacturers intend to affect the structure and function of the body.

In addition to this industry-wide evidence of intended use, the record contains numerous documents from the nation's largest smokeless tobacco manufacturer, UST. The UST documents in the record show that:

- UST officials in the early 1970's recommended the development of products with "three different . . . strengths of nicotine[:] . . . a. High nicotine, strong tobacco flavor . . . b. Medium strength of nicotine . . . c. Low nicotine, sweet product." In particular, UST officials recommended the development of a product that provided "mild" nicotine satisfaction targeted at "new users . . . age group 15-35."

- Shortly after these recommendations, UST began aggressively to market low-nicotine products, targeted "for you guys just starting out." Marketing techniques included free sampling on college campuses and at sports events. Advertisements included instructions on use for new users.

- Numerous UST documents and statements refer to an explicit "graduation process" in which users of smokeless tobacco are encouraged to start with low-nicotine starter brands and then progress to higher nicotine brands. For

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instance, a UST vice president has stated that Skoal Bandits, one of UST's low-nicotine brands, "is the introductory product, and we look towards establishing a normal graduation process."

These UST documents confirm that smokeless tobacco manufacturers deliberately produce brands with a range of nicotine deliveries in order to allow users to progress (or "graduate") from low-delivery products to high-delivery products. They thus corroborate the Agency's finding that smokeless tobacco is intended to affect the structure and function of the body.

E. The "Intended Use" of a Product Is Not Determined Only on the Basis of Promotional Claims

The principal legal argument of the tobacco industry is that the intended use of a product must be determined exclusively on the basis of the promotional claims made by the manufacturer. Under the industry's legal theory, the Agency must disregard the voluminous internal tobacco industry documents showing that the manufacturers have in mind, and design their products to provide, the pharmacological effects of nicotine. The tobacco industry also urges the Agency to disregard the evidence of the foreseeable pharmacological effects and uses of cigarettes and smokeless tobacco, as well as the evidence of the actual consumer use of these products for pharmacological purposes.

The Agency rejects the industry's legal argument. First, the industry's position is contrary to the plain language of the Act. The Act does not say that only products "promoted" to affect the structure or function of the body are drugs or devices. Rather, the Act says that products "intended" to affect the structure or function of the body are drugs or devices. The plain meaning of "intend" is significantly broader than the meaning of "promote." As summarized above, the plain meaning of "intend" includes "to have in

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mind" and "to design" for a particular use. The evidence that is relevant to determining the uses that a manufacturer "has in mind" or "designs" includes not just the promotional claims of the manufacturer, but also the internal statements of the manufacturer, as well as the manufacturer's research and actions. Moreover, the ordinary meaning of "intend" also encompasses the reasonably foreseeable consequences of the manufacturer's actions, thereby making consideration of the foreseeable pharmacological effects and uses of a product relevant to its intended use.

Second, the industry's position is contrary to FDA's regulations. These regulations provide that the term "intended use" refers to the "objective intent" of the manufacturer. Under these regulations, the Agency determines the intent of the manufacturer objectively by evaluating all of the relevant evidence in the record from the perspective of a reasonable fact-finder. FDA's regulations expressly direct the Agency to consider the manufacturer's "knowledge" of the use of the product; the manufacturer's "expressions" and "oral or written statements"; and the "circumstances surrounding the distribution of the article." 21 CFR 201.128, 801.4. Thus, the regulations expressly provide that the Agency should consider a broad range of evidence in determining intended use, not merely the manufacturer's promotional claims.

Third, the industry's position is contrary to judicial decisions interpreting the Act. These decisions have applied the Act's definitions of drug and device to two different types of products. The first type of product is one that contains no known drug ingredients and has no known pharmacological effects or uses. In cases involving such products, the courts recognize that a manufacturer's promotional claims have a crucial

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role in establishing intended use. Even a product like mineral water can be brought within FDA's jurisdiction by advertisements that make pharmacological claims. *See Bradley v. United States*, 264 F. 79 (5th Cir. 1920).

The situation is fundamentally different, however, when the product contains a known drug ingredient like nicotine that has known pharmacological effects and uses. When a product is pharmacologically active, the courts have recognized that "a fact finder should be free to pierce . . . a manufacturer's misleading . . . labels to find actual therapeutic intent on the basis of objective evidence." *National Nutritional Foods Ass'n v. FDA*, 504 F.2d 761, 789 (2d Cir. 1974). Thus, contrary to the industry's contention, the courts have recognized that in determining intended use, FDA may consider a wide range of evidence beyond the manufacturer's promotional claims, including evidence of the pharmacological effects of the product, *e.g., United States v. Undetermined Quantities . . . "Pets Smellfree."* 22 F.3d 235, 240 (10th Cir. 1994); the purposes for which consumers actually use the product, *e.g., ASH*, 655 F.2d at 239-240; the medical use of the product, *e.g., United States v. An Article of Device . . . Toftness Radiation Detector*, 731 F.2d 1253, 1257 (7th Cir. 1984); and how the product was formulated, *e.g., American Health Products Co. v. Hayes*, 574 F. Supp. 1498, 1508 (S.D.N.Y. 1983).

Fourth, the industry's position is contrary to FDA's administrative precedent. In a broad range of instances, FDA has asserted jurisdiction over products based on the likely pharmacological effects and uses of the product—not express promotional claims. Indeed, in many of these instances, the manufacturer's promotional claims were designed to disguise the actual intended use of the product.

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Fifth, the industry's position is contrary to the public health objectives of the Act. If promotional claims alone determined the intended use of a product, virtually any manufacturer of drugs or devices could avoid the Act's reach by simply refraining from making pharmacological claims for the product. For instance, under the industry's interpretation, a company could market a potent tranquilizer or amphetamine for its "pleasurable" effect and escape FDA regulation. To protect the public from the unregulated distribution of products with pharmacologically active ingredients, the Agency must be able to look beyond a manufacturer's promotional claims when determining whether to regulate such products.

For these reasons, the Agency rejects the tobacco industry's legal theory that intended use is determined exclusively on the basis of promotional claims. The Agency also rejects the premise of the industry's position—namely, that their promotional claims demonstrate that cigarettes and smokeless tobacco are not intended to affect the structure and function of the body. To the contrary, as internal tobacco company documents indicate, promises of "satisfaction" in tobacco advertisements imply that cigarettes and smokeless tobacco will provide consumers with desired pharmacological effects of nicotine. These implied drug claims lend support to the Agency's finding that cigarettes and smokeless tobacco are intended to affect the structure and function of the body.

F. Response to Additional Comments

This section responds to additional comments regarding the evidence of the intended use of cigarettes and smokeless tobacco and the Agency's use of this evidence.

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G. Considered Cumulatively, the Evidence Overwhelmingly Demonstrates that Cigarettes and Smokeless Tobacco Are Intended to Affect the Structure and Function of the Body

As summarized above, the evidence in the record provides several independent bases for the Agency's finding that cigarettes and smokeless tobacco are "intended" to affect the structure and function of the body. Independently, each of these distinct categories of evidence is a strong and sufficient basis for the Agency's conclusion that the manufacturers of cigarettes and smokeless tobacco intend the pharmacological effects and uses of their products. Considered together, they are mutually corroborating. Both independently and taken as a whole, therefore, the evidence in the administrative record overwhelmingly establishes that cigarettes and smokeless tobacco are "intended to affect the structure or any function of the body" within the meaning of the Act.

III. Cigarettes and Smokeless Tobacco Are Combination Products Consisting of "Drug" and "Device" Components

The Agency's findings in sections I and II establish that the nicotine in cigarettes and smokeless tobacco is a "drug" under section 201(g)(1)(C) of the Act. These findings show that the nicotine in cigarettes and smokeless tobacco "affect[s] the structure or any function of the body" and that these effects are "intended." These findings thus demonstrate that the nicotine in cigarettes and smokeless tobacco meets the statutory definition of a "drug."

Cigarettes and smokeless tobacco are not simply packaged nicotine, however. They also include delivery devices that deliver nicotine to the body. Section 201(h)(3), 21 U.S.C. 321(h)(3). In the case of cigarettes, the device components work together upon combustion outside the body to form a nicotine-containing aerosol, which then delivers

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nicotine to the body when inhaled by the smoker. In the case of smokeless tobacco, the device components function by presenting nicotine to the consumer in a form that is palatable and absorbable by the buccal mucosa. Unlike the drug nicotine, these device components achieve their primary intended purpose without chemical action in or on the body and without being metabolized.

The presence of both drug and device components in cigarettes and smokeless tobacco make these products "combination products" under section 503(g) the Act, 21 U.S.C. 353(g)(1).

IV. FDA's Assertion of Jurisdiction Over Cigarettes and Smokeless Tobacco at This Time Is Justified

FDA has always exercised jurisdiction over tobacco products when there is sufficient evidence in the record to establish that these products are "intended" to treat or prevent disease or to affect the structure or function of the body. Over thirty years ago, for instance, the Agency asserted jurisdiction over a brand of cigarettes when the evidence established that the brand was intended to reduce body weight. *United States v. 354 Bulk Cartons . . . Trim Reducing-Aid Cigarettes*, 178 F. Supp. 847 (D.N.J. 1959).

The Agency last considered whether to regulate cigarettes in the late 1970's, when the Agency rejected petitions by Action on Smoking and Health (ASH) urging the Agency to regulate cigarettes as drugs or devices. The Agency agreed with ASH that "objective evidence other than manufacturers' claims can be material to a determination of intended use" and that "evidence of consumer use can be one element of objective evidence to be weighed in determining if the intended purpose of a product subjects it to regulation under the Act." However, the Agency concluded that the evidence presented by ASH in the

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petition was insufficient to establish that cigarettes and smokeless tobacco were in fact intended to affect the structure and function of the body. The court deferred to the Agency's determination not to regulate cigarettes as drugs but expressly left open the possibility that FDA might, at a later date, revisit its decision and determine that it did indeed have jurisdiction over cigarettes. *ASH v. Harris*, 655 F.2d 236 (D.C. Cir. 1980).

The evidence regarding the intended use of cigarettes and smokeless tobacco has changed dramatically since *ASH*. First, a scientific consensus has emerged since 1980 that nicotine is addictive and has other significant pharmacological effects and that cigarettes and smokeless tobacco are used by consumers to obtain pharmacological effects. As summarized above, no major public health organization had determined that nicotine was an addictive drug before 1980. Between 1980 and 1994, however, every leading scientific organization with expertise in addiction concluded that nicotine is addictive. This new evidence thus shows that the pharmacological effects and uses of cigarettes and smokeless tobacco have become foreseeable.

Second, scientific evidence accumulated since 1980 has shown that the vast majority of people who use cigarettes and smokeless tobacco use these products to satisfy addiction or to obtain other pharmacological effects. As summarized above, this new evidence now shows that 77% to 92% of smokers are addicted to nicotine and provides a basis for estimating that 75% of young regular smokeless tobacco users are addicted to nicotine. This new evidence establishes that consumers use cigarettes and smokeless tobacco predominantly for pharmacological purposes.

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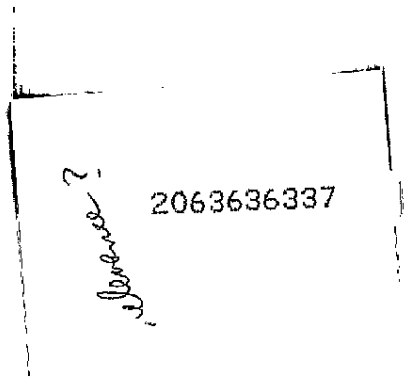

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Third, FDA, congressional, and other investigations have recently uncovered a wealth of documents from a wide range of tobacco companies that show that the manufacturers have long known of the pharmacological effects and uses of nicotine and have designed their products to provide pharmacologically active doses of nicotine to consumers. Virtually none of this information was available to FDA in 1980.

Information developed since 1980 also demonstrates that the Agency has a unique public health opportunity to reduce substantially the more than 400,000 deaths from tobacco use each year in the United States. This information shows that for most people tobacco use and nicotine addiction begin in childhood and adolescence, and that an increasing number of American children and adolescents are using cigarettes and smokeless tobacco. The data now suggest that if children and adolescents can be prevented from initiating tobacco use during their teenage years, they are unlikely to begin tobacco use later in life, thereby preventing the onset of tobacco-related disease and premature death.

Before the importance of youth-centered interventions was identified, most of the regulatory approaches available under the Federal Food, Drug, and Cosmetic Act to address tobacco-related disease and death, such as removal of the products from the market, were not believed to be feasible solutions. It is now apparent, however, that FDA's authority to restrict the sale, distribution, and use of cigarettes and smokeless tobacco to people under the age of eighteen is an effective tool to reduce the adverse health consequences of tobacco use. Thus, asserting jurisdiction over cigarettes and

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smokeless tobacco now presents an opportunity to use the Agency's resources effectively for substantial public health gains.

The court in *ASH* specifically recognized that FDA was permitted to modify its position and that any new FDA position would be accorded deference by the courts. *Id.* at 242 n.10. In light of the substantial new information, FDA has reviewed its earlier determination not to assert jurisdiction over tobacco products. The new evidence persuades the Agency to conclude that its previous position is no longer consistent with the relevant facts and should be changed. The evidence before the Agency is now sufficient to establish that cigarettes and smokeless tobacco are in fact intended to affect the structure and function of the body.

V. *Congress Has Not Precluded or Preempted FDA from Regulating Cigarettes and Smokeless Tobacco*

FDA disagrees with the comments of the tobacco industry that assert that Congress has precluded or preempted FDA from regulating cigarettes and smokeless tobacco. The plain language of the Act does not exclude cigarettes or smokeless tobacco from FDA jurisdiction. Tobacco products are expressly excluded from the jurisdiction of the Consumer Product Safety Commission under the Federal Hazardous Substances Act and from the jurisdiction of the Environmental Protection Agency under the Toxic Substances Control Act. The absence of any similar exclusion in the Federal Food, Drug, and Cosmetic Act demonstrates that Congress has not chosen to exclude cigarettes and smokeless tobacco from FDA jurisdiction.

The legislative history of the Act confirms that the Act should not be interpreted to preclude FDA jurisdiction over tobacco products. Congress has long known that FDA

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will assert jurisdiction over cigarettes when the evidence establishes that the cigarettes are intended to affect the structure or function of the body. For instance, FDA asserted jurisdiction more than 30 years ago over cigarettes that were intended to reduce weight. This demonstrates that Congress has not "ratified" or "acquiesced in" an interpretation of the Act that would preclude FDA from regulating tobacco products intended to affect the structure or function of the body.

Moreover, even if Congress had acquiesced in such an interpretation of the Act, congressional acquiescence in a prior agency interpretation does not prevent an agency from changing its interpretation. *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 45 (1983). In the case of cigarettes and smokeless tobacco, a change in interpretation would be justified by the new evidence in the record—evidence never previously before either the Agency or Congress.

The Agency also disagrees that other federal statutes preempt FDA jurisdiction over cigarettes and smokeless tobacco. Both the Federal Cigarette Labeling and Advertising Act and the Comprehensive Smokeless Tobacco Health Education Act have provisions that expressly specify the limited extent to which these laws preempt FDA and other federal agencies from regulating cigarettes or smokeless tobacco. In the Federal Cigarette Labeling and Advertising Act, for instance, federal agencies are preempted only from requiring "statement[s] relating to smoking and health . . . on any cigarette package." 15 U.S.C. 1334(a). The narrow preemption provisions that Congress expressly included in these statutes do not apply to FDA's assertion of jurisdiction over cigarettes and smokeless tobacco.

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No other federal statutes contain provisions preempting FDA regulation of tobacco products. In the absence of an express preemption provision, one federal statute preempts another federal statute only where there is an irreconcilable conflict between the two laws. *Connecticut Nat'l Bank v. Germain*, 503 U.S. 249, 253 (1992). There is no irreconcilable conflict between FDA jurisdiction and other federal statutes.

VI. *FDA Employed Procedures That Provided an Opportunity for Full Public Participation and Exceeded All Legal Requirements*

FDA went to great lengths to involve the public in the process by which the Agency made its final jurisdictional determination. The Commissioner made public his intention to investigate the role of nicotine in tobacco products, testified twice before Congress on the Agency's findings, wrote to all the major cigarette and tobacco companies requesting information on the role of nicotine in their products, and held a public advisory committee meeting on the abuse potential of nicotine. Although the Agency is not required to undertake rulemaking to establish jurisdiction over new products, the Agency published in the *Federal Register* its initial jurisdictional findings and comprehensive legal analysis in a 325-page document, supported by over 600 footnotes, and sought public comment on those findings. The Agency placed over 210,000 pages of supporting documents in a public docket. FDA received over 700,000 comments on the Jurisdictional Analysis and the accompanying proposed rule. The Agency has responded to substantive comments in this Annex and in the preamble to the Final Rule.

FDA disagrees with the comments of the tobacco industry that the record supporting the Jurisdictional Analysis or the procedures the Agency followed were inadequate. The procedures the Agency employed in reaching its final determination

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exceeded the requirements of the Administrative Procedures Act (APA) and the Agency's own procedural requirements.

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INTRODUCTION

On August 11, 1995, the Food and Drug Administration (hereinafter FDA or the Agency) announced the results of its extensive investigation and comprehensive legal analysis regarding the Agency's jurisdiction over cigarettes and smokeless tobacco in a document entitled, "Nicotine in Cigarettes and Smokeless Tobacco Products Is a Drug and These Products Are Nicotine Delivery Devices Under the Federal Food, Drug, and Cosmetic Act" (hereinafter referred to as the "Jurisdictional Analysis"). 60 FR 41453–41787 (Aug. 11, 1995). The Agency reported that its investigation and analysis supported a finding at that time that nicotine in cigarettes and smokeless tobacco is a drug and that these products are drug delivery devices within the meaning of the Federal Food, Drug, and Cosmetic Act (hereinafter the Act). Because of the unique importance of the jurisdictional issue, the Agency invited comment on this finding.

The public comment period closed on January 2, 1996. 60 FR 53620 (Oct. 16, 1995). On March 20, 1996, the Agency published in the *Federal Register* notice of an additional 30 day comment period, until April 19, 1996, limited to specific documents the Agency added to the docket in support of the Agency's analysis of jurisdiction. 61 FR 11419 (Mar. 20, 1996). The Agency received over 700,000 comments on its Jurisdictional Analysis and its Proposed Rule restricting the sale and distribution of cigarettes and smokeless tobacco to protect children and adolescents. The Agency has carefully considered these comments.

This final jurisdictional determination responds to the public comments and reports the Agency's conclusion that the nicotine in cigarettes and smokeless tobacco is a drug and that cigarettes and smokeless tobacco are drug delivery devices whose purpose is to

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deliver nicotine to the body in a manner in which it can be readily absorbed. These products, therefore, are subject to FDA regulation under the Act.

The legal question of whether cigarettes and smokeless tobacco are drugs and devices subject to FDA regulation is one that "FDA has jurisdiction to decide with administrative finality." *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 653 (1973). The Act defines a "drug" as (1) an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals," or (2) an article (other than food) "*intended to affect the structure or any function of the body of man or other animals.*" Section 201(g)(1)(B) and (C), 21 U.S.C. 321(g)(1)(B) and (C) (emphasis added). The Act's device definition parallels the drug definition and provides that an instrument, apparatus, or other similar article is a "device" if it is (1) "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals," or (2) "*intended to affect the structure or any function of the body of man or other animals.*" Section 201(h)(2) and (3), 21 U.S.C. 321(h)(2) and (3) (emphasis added). These definitions are intended to be broad in scope and to encompass products that are not within the ordinary medical definitions of drugs and devices. *See United States v. An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 793 (1969) ("we think it plain that Congress intended to define 'drug' far more broadly than does the medical profession").

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In applying these legal standards to cigarettes and smokeless tobacco, the Agency has focused on the second prong of the definition of drug and device: whether cigarettes and smokeless tobacco are "intended to affect the structure or any function of the body." Historically, the Agency has regulated tobacco products whenever the evidence before the

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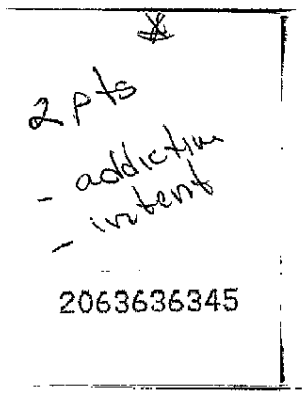

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Agency was sufficient to establish that the products were intended to affect the structure or function of the body. FDA last considered whether cigarettes were drugs or devices in the late 1970's, determining that the limited evidence then before the Agency was insufficient to demonstrate that these products were intended to affect the structure or function of the body. *See Action on Smoking and Health v. Harris*, 655 F.2d 236 (D.C. Cir. 1980). Since that time, substantial new evidence has become available to FDA. This evidence includes the emergence of a scientific consensus that cigarettes and smokeless tobacco cause addiction to nicotine and the disclosure of thousands of pages of internal tobacco company documents detailing that the manufacturers intend to affect the structure and function of the human body.

The determination whether a product is subject to FDA jurisdiction often requires the Agency to make difficult factual judgments, including judgments regarding the intended use of the product. The Agency must have enough evidence to show that these factual judgments are rational and not "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. 706(2)(A); *see National Nutritional Foods Ass'n v. Weinberger*, 512 F.2d 688, 700-701 (2d Cir. 1975), *cert. denied*, 423 U.S. 827 (1975). The Agency must provide some evidentiary support for its factual judgments, and there must be a rational connection between these judgments and the conclusions reached. *Motor Vehicle Mfrs. Ass'n of the United States, Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42-43 (1983). The Agency should also have considered all the relevant data and the relevant aspects of the issue. *Id.*; *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971). An agency's factual judgments made in the context of an informal agency action ordinarily need only be supported by a record that

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shows a "rational basis" for the agency's decision, *Natural Resources Defense Council, Inc. v. EPA*, 16 F.3d 1395, 1401 (4th Cir. 1993), or by a record consisting of "some evidence" in support of the agency's decision. *Aman v. FAA*, 856 F.2d 946, 950 n.3 (7th Cir. 1988) (while an agency determination need only have "some evidentiary basis to avoid being held 'arbitrary and capricious,' [t]he difference between 'some' and 'substantial' probably cannot be precisely stated except in the context of particular cases. . . ."). Several courts, however, have held that an agency's factual judgments must always be supported by "substantial evidence," even though that standard is intended to be applied only to formal "on the record" agency actions, *see* 5 U.S.C. 706(2)(E).[1]

In this case, the Agency's evidentiary record exceeds these standards. That is, FDA has concluded that the evidence now before the Agency supports a finding of jurisdiction over these products. In assessing the new evidence, FDA has used a two-step approach, evaluating first whether the nicotine in these products "affects the structure or

[1] *See, e.g., Ass'n of Data Processing Service Organizations, Inc. v. Board of Governors*, 745 F.2d 677, 683-684 (D.C. Cir. 1984) (Scalia, J) ("When the arbitrary or capricious standard is performing that function of assuring factual support, there is no substantive difference between what it requires and what would be required by the substantial evidence test, since it is impossible to conceive of a 'nonarbitrary' factual judgment supported only by evidence that is not substantial in the APA sense . . . ."). *Contra Corrosion Proof Fittings v. EPA*, 947 F.2d 1201, 1213-1214 and n.17 (5th Cir. 1991) (declining to find that the substantial evidence standard and the arbitrary and capricious standard "are in fact one and the same"); *Am. Paper Inst. v. Am. Elec. Power Serv. Corp.*, 461 U.S. 402, 412 n.7 (1983) (in the absence of a specific command in the statute to employ a particular standard of review, the Court of Appeals should have applied the more lenient arbitrary and capricious standard in evaluating the factual basis supporting an agency's informal rulemaking).

The difference in the case law, however, is of no consequence here because FDA's evidentiary record exceeds the "substantial evidence" standard—the more stringent of the two standards. Substantial evidence is "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Consolo v. Federal Maritime Commission*, 383 U.S. 607, 619-620 (1966) (quoting *Consolidated Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938)), even if two inconsistent conclusions might be inferred from the same evidence. *See Consolo*, 383 U.S. at 620; *NLRB v. Nevada Consolidated Copper Corp.*, 316 U.S. 105, 106 (1942). Under the substantial evidence standard, an agency's factual determinations are conclusive even if supported by "something *less than the weight of the evidence* . . . ." *Consolo*, 383 U.S. at 620 (emphasis added).

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any function of the body" and second whether these effects are "intended." FDA has determined that the evidence overwhelmingly demonstrates that (1) nicotine in cigarettes and smokeless tobacco has significant effects on the structure and function of the body and (2) these effects are intended by the manufacturers of these products.

The Agency's determination that nicotine in cigarettes and smokeless tobacco "affect[s] the structure or any function of the body" is based on three central findings:

1. Nicotine in cigarettes and smokeless tobacco causes and sustains addiction.

2. Nicotine in cigarettes and smokeless tobacco causes other psychoactive (mood-altering) effects, including tranquilization and stimulation.

3. Nicotine in cigarettes and smokeless tobacco controls weight.

These findings demonstrate that nicotine in cigarettes and smokeless tobacco has the same pharmacological effects as other drugs that FDA has traditionally regulated, including tranquilizers, stimulants, appetite suppressants, and products used in the maintenance of addiction such as methadone. Thus, the effects of nicotine in cigarettes and smokeless tobacco on the structure and function of the body are within FDA's jurisdiction.

FDA's determination that the manufacturers of cigarettes and smokeless tobacco "intend" the effects of nicotine on the structure and function of the body is based on five central findings:

1. The addictive and other pharmacological effects of nicotine are so widely known and accepted that it is foreseeable to a reasonable manufacturer that cigarettes and smokeless tobacco will cause addiction to nicotine and other significant pharmacological effects and will be used by

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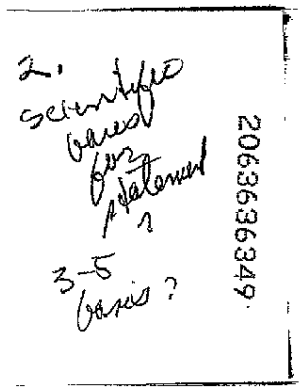

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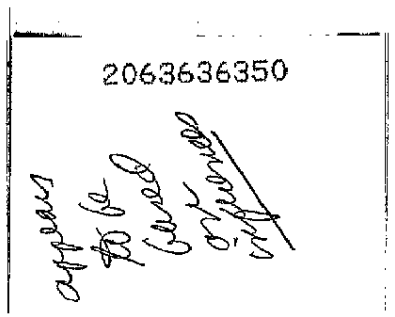

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consumers for pharmacological purposes, including sustaining their addiction to nicotine.

2. Consumers use cigarettes and smokeless tobacco predominantly for pharmacological purposes, including sustaining their addiction to nicotine, mood alteration, and weight loss.

3. Manufacturers of cigarettes and smokeless tobacco know that nicotine in their products causes pharmacological effects in consumers, including addiction to nicotine and mood alteration, and that consumers use their products primarily to obtain the pharmacological effects of nicotine.

4. Manufacturers of cigarettes and smokeless tobacco design their products to provide consumers with a pharmacologically active dose of nicotine.

5. An inevitable consequence of the design of cigarettes and smokeless tobacco to provide pharmacologically active doses of nicotine is to keep consumers using cigarettes and smokeless tobacco by sustaining their addiction to nicotine.

Each of these findings provides an independent basis for establishing that the manufacturers of cigarettes and smokeless tobacco "intend" to affect the structure and function of the body. Taken together, the cumulative weight of the evidence convincingly supports the determination that the effects of nicotine on the structure and function of the body are "intended" by the manufacturers.

FDA's assertion of jurisdiction over cigarettes and smokeless tobacco is consistent with the Agency's assertion of jurisdiction over other similar products. FDA regulates a diverse range of products under the Act. These products—foods, drugs, devices, cosmetics, and radiation-emitting electronic products—all "affect the health and well-being of the public." *United States v. Park*, 421 U.S. 658, 672 (1975). The common feature that distinguishes these products is their intimate and potentially harmful contact

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with the human body. *See id.* at 668. FDA-regulated products include those that are intended to be ingested, inhaled, applied to the skin, implanted, or otherwise used in close contact with the body. Cigarettes, which deliver a pharmacologically active dose of nicotine to the body through inhalation, and smokeless tobacco, which delivers a pharmacologically active dose of nicotine through buccal absorption, share this distinguishing feature and thus are properly subject to FDA jurisdiction.

The determinations that (1) the nicotine in cigarettes and smokeless tobacco "affects the structure or any function of the body" and (2) these effects are "intended" by the manufacturers satisfy the legal requirements under the Act for FDA jurisdiction. FDA has also determined that cigarettes and smokeless tobacco contain both a "drug" and a "device" and are thus combination products within the meaning of the Act. Accordingly, the Agency has concluded that the nicotine in cigarettes and smokeless tobacco is a drug and that cigarettes and smokeless tobacco are drug delivery devices under the Federal Food, Drug, and Cosmetic Act.

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I. CIGARETTES AND SMOKELESS TOBACCO "AFFECT THE STRUCTURE OR ANY FUNCTION OF THE BODY" WITHIN THE MEANING OF THE ACT

In the Jurisdictional Analysis, FDA found, based on the evidence available to it at the time, that nicotine in cigarettes and smokeless tobacco is "highly addictive, causes other psychoactive effects, such as relaxation and stimulation, and affects weight regulation." *See* Jurisdictional Analysis, 60 FR 41464 (Aug. 11, 1995). The Agency found that the nicotine in these products "has pharmacological effects on both the structure and function of the central nervous system, particularly the brain," and that "[a]ddiction is a direct result of nicotine's effects on the structure and function of the body." *Id.* at 41470. Based on these findings of pharmacological effects, the Agency found that cigarettes and smokeless tobacco "*affect the structure or any function of the body.*" *Id.* (emphasis added).

As described more fully below, the Agency received comments that agreed and disagreed with the Agency's position.[2] After considering the evidence in the administrative record,[3] including the public comments, the Agency finds that cigarettes and

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[1] The Agency received a consolidated comment of the cigarette industry (Brown & Williamson Tobacco Corp., Liggett Group Inc., Lorillard Tobacco Co., Philip Morris Inc., R.J. Reynolds Tobacco Co., Tobacco Institute Inc.) (Jan. 2, 1996) (hereinafter Joint Comments of the Cigarette Manufacturers). *See* AR (Vol. 535 Ref. 96). The Agency also received a consolidated comment of the smokeless tobacco industry (Smokeless Tobacco Council. Inc., Brown & Williamson Tobacco Corp., Conwood Co., L.P., National Tobacco Co., L.P., the Pinkerton Tobacco Co., R.C. Owen Co., Swisher International, Inc., United States Tobacco Co.) (Jan. 2, 1996) (hereinafter Joint Comments of the Smokeless Tobacco Manufacturers). *See* AR (Vol. 526 Ref. 95).

[3] In the footnotes of this document, cites to the administrative record (AR) specify both the number of the reference and the volume of the AR in which the reference is found. The reference may contain the full document or a partial document. Where the reference contains a partial document, the full document may be found elsewhere in the AR. In a small number of cases, a reference will occupy several volumes of the AR. for example, the Joint Comments of the Cigarette Manufacturers. In these cases, the cite will specify the volume of the AR in which the reference begins.

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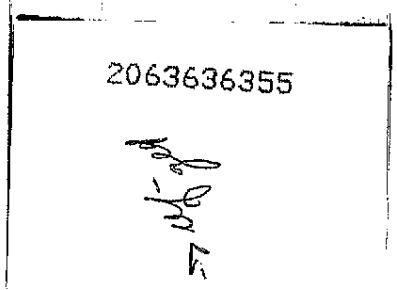

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smokeless tobacco do indeed "affect the structure or any function of the body" within the meaning of sections 201(g)(1)(C) and 201(h)(3) of the Act, 21 U.S.C. 321(g)(1)(C), 321(h)(3).

To interpret the Federal Food, Drug, and Cosmetic Act in a manner that excludes the effects of these products from the scope of the structure-function prong of the drug and device definitions would be inconsistent with the plain meaning of the Act, its legislative history, case law interpreting the structure-function prong, and the Agency's past applications of that provision. The Agency's conclusions are summarized in section I.A., followed by a detailed discussion of the comments and the Agency's responses to them in section I.B.

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A. THE PHARMACOLOGICAL EFFECTS OF THE NICOTINE IN CIGARETTES AND SMOKELESS TOBACCO ON THE BODY ARE SIGNIFICANT

Cigarettes and smokeless tobacco contain nicotine, an addictive and pharmacologically active drug. *See* section II.A., below. Nicotine is the active ingredient in several products regulated as drugs by the Agency, including nicotine transdermal patches, nicotine chewing gums, nicotine nasal spray, and Favor, a hollow paper tube with nicotine impregnated in the mouthpiece. *See* Jurisdictional Analysis, 60 FR 41482, 41549-41550. The effects of the nicotine in cigarettes and smokeless tobacco greatly exceed those exerted by the nicotine-containing products already regulated by the Agency.[4]

Nicotine in cigarettes and smokeless tobacco produces significant pharmacological effects on the human body. First, nicotine causes and sustains addiction. The processes

[4] Nicotine-use cessation products are discussed in section II.A.5., below.

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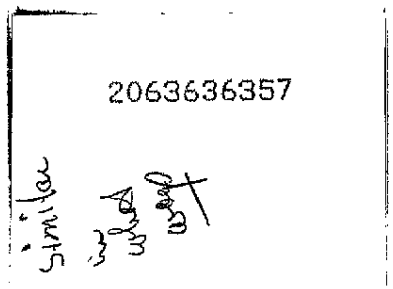

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that lead to addiction to nicotine in cigarettes and smokeless tobacco are similar to those that lead to addiction to products such as morphine and opium. *See* section II.A.2., below. Like other addictive substances, nicotine in cigarettes and smokeless tobacco achieves its addictive effects by exerting psychoactive, or mood-altering, effects on the brain and by producing chemical reactions in the brain that motivate repeated, compulsive use of the substance. *See* section II.A.3., below. These pharmacological effects create dependence in the user. *Id.*

In addition to creating and sustaining addiction, cigarettes and smokeless tobacco produce other significant pharmacological effects. For example, under some circumstances, nicotine in cigarettes and smokeless tobacco has a sedating or tranquilizing effect on mood and brain activity. *See* section II.A.4., below. Under other circumstances, nicotine in cigarettes and smokeless tobacco has a stimulant or arousal-increasing effect on the body. *Id.*

Nicotine in cigarettes and smokeless tobacco also controls body weight. *Id.* Clinical and animal studies indicate that nicotine administration causes weight loss and that cessation of nicotine administration results in weight gain. *Id.*

These effects on the structure and function of the body are significant and quintessentially drug-like. They produce immediate pharmacological changes in the function of the brain (depressing or stimulating arousal); they change the physical structure of the body (increased growth of nicotine receptors in the brain, weight loss); and they cause drug dependence (addiction). *Id.*

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The tobacco industry comments argue that "remote" or "insignificant" pharmacological effects are not subject to FDA jurisdiction. Although "remote physical effect[s] upon the body" may not be covered by the structure-function provision, *see E.R. Squibb & Sons, Inc. v. Bowen*, 870 F.2d 678, 682 (D.C. Cir. 1989), the pharmacological effects of cigarettes and smokeless tobacco are not "remote" or insignificant. Indeed, they are powerful and immediate pharmacological effects that are not qualitatively or quantitatively different from the effects of other drugs subject to FDA jurisdiction.

In fact, the effects of cigarettes and smokeless tobacco—addiction, sedation, stimulation, and weight loss—are precisely the types of effects the Agency traditionally regulates. It is well established that the Agency has the authority to regulate, and has regulated, products that sedate, tranquilize, or reduce anxiety (e.g., Valium and other benzodiazepines); products that stimulate or restore mental alertness (e.g., caffeine-containing pills such as NoDoz, *see* Stimulant Drug Products for Over-the-Counter Human Use, Final Monograph, 53 FR 6100 (February 29, 1988); 21 CFR Part 340);[5] products that cause weight loss (*see* Weight Control Products for Over-the-Counter Human Use, Certain Active Ingredients, 56 FR 37792 (August 8, 1991); 21 CFR 310.545(a)(20); *see also United States v. 354 Bulk Cartons . . . Trim Reducing-Aid Cigarettes*, 178 F. Supp. 847, 851 (D.N.J. 1959)); and products that are used for maintenance treatment of addiction (e.g., methadone and other "narcotic drugs [used] in the medical treatment of narcotic addiction," 21 CFR 291.501). The approved uses of these products include uses to "affect the structure or any function of the body" under

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[5] A more detailed discussion of the Agency's regulation of caffeine and caffeine-containing products is contained in section I.B., below.

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section 201(g)(1)(C) of the Act. Thus, cigarettes and smokeless tobacco have the same effects as products that are undeniably within FDA's jurisdiction.

Indeed, internal tobacco company documents reveal that tobacco industry scientists understand that the nicotine in tobacco produces pharmacological effects no different from those produced by approved drugs. These industry scientists viewed prescription drugs as competing products.[6] Over three decades ago, the British American Tobacco Company (BATCO), the parent of Brown & Williamson Tobacco Corporation, commissioned a study to compare the effects of nicotine with those of tranquilizers, "which might supersede tobacco habits in the near future."[7] The study concluded that nicotine was "more beneficial or less noxious—than the new tranquilizers" because it reduced stress and regulated weight.[8]

Philip Morris and R.J. Reynolds Tobacco Company (RJR) also have repeatedly compared the effects of nicotine from tobacco to the effects of drugs regulated by FDA. For example, Philip Morris researchers and officials have concluded that smokers use cigarettes as "a narcotic, tranquilizer, or sedative"[9] and that "[nicotine] is a physiologically active, nitrogen containing substance. *Similar organic chemicals include . . . quinine,*

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[6] These documents, and the conclusions the Agency has drawn from them, are described in detail in sections II.C. and II.D., below.

[7] Haselbach CH, Liberi O. *Final Report on Project HIPPO II* (Geneva: Battelle Memorial Institute, International Division, Mar. 1963), at 1. *See* AR (Vol. 64 Ref. 321).

[8] *Id.* at 2.

[9] Udow A. *Why People Start to Smoke* (Jun. 2, 1976), in 141 Cong. Rec. H7664 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

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cocaine, atropine and morphine. While each of these substances can be used to affect human physiology, *nicotine has a particularly broad range of influence."*[10]

Similarly, RJR scientists have reported that smokers who inhale lightly appear to use tobacco to achieve "mental activation and performance enhancement" whereas those who inhale more deeply show brain effects that "may reflect the anxiolytic properties of benzodiazepines,"[11] prescription drugs used to alleviate anxiety. Another RJR researcher has stated:

> [I]n different situations and at different dose levels, *nicotine appears to act as a stimulant, depressant, tranquilizer, psychic energizer, appetite reducer, anti-fatigue agent, or energizer. . . .* Therefore, in addition to competing with products of the tobacco industry, *our products may, in a sense, compete with a variety of other products with certain types of drug action.*[12]

Thus, the industry's own documents acknowledge that the pharmacological effects of their products are the same as the effects the Agency has considered to be structure-function effects within the meaning of section 201(g)(1)(C). Notwithstanding the views of their own scientists, the tobacco industry comments publicly assert that cigarettes and smokeless tobacco do not affect the structure or any function of the body within the meaning of the Act because their effects are too "remote" or not therapeutic or beneficial.

The ramifications of the tobacco industry's position are far-reaching. If the Agency were to determine that the pharmacological effects of cigarettes and smokeless

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[10] Philip Morris Inc., Draft Report Regarding a Proposal for a "Safer" Cigarette, Code-named *Table* (emphasis added). *See* AR (Vol. 531 Ref. 122).

[11] Pritchard WS, R.J. Reynolds Tobacco Co., Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485, at 488. *See* AR (Vol. 3 Ref. 23-2).

[12] Teague CE, R.J. Reynolds Tobacco Co., *Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of Nicotine Therein* (Apr. 14, 1972), at 1-2 (emphasis added). *See* AR (Vol. 531 Ref. 125).

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tobacco are not effects on the structure and function of the body, or are not significant effects, the Agency's authority to regulate other products with like pharmacological effects—sedation, stimulation, weight loss, and satisfaction of addiction—would be called into question. Under the industry's characterization of the effects of their products, even if the pharmacological effects of sedation, stimulation, weight loss, or satisfaction of addiction were expressly promoted or otherwise intended, products producing the same effects could not be regulated under section 201(g)(1)(C) or 201(h)(3) because, by the industry's definition, these products would not "affect the structure or any function of the body." This view, if accepted, could undermine the Agency's ability to regulate drugs and devices that are not used in the diagnosis or treatment of disease, but significantly affect the structure or any function of the body. Further, such an interpretation would be inconsistent with over 50 years of Agency practice since passage of the Act in 1938.

In sum, cigarettes and smokeless tobacco do affect the structure and function of the body within the meaning of the Act. The pharmacological effects of nicotine-containing tobacco products are significant and the same as the effects of other products traditionally regulated by FDA. Because these effects are "intended" within the meaning of the Act—the issue discussed in section II., below—cigarettes and smokeless tobacco fall within the jurisdiction of the Agency under the Act.

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B. RESPONSE TO COMMENTS

1. As noted in section I.A., above, tobacco industry comments and others argue that the effects of nicotine delivered from cigarettes and smokeless tobacco are too remote or insignificant to be subject to the Act. These comments minimize nicotine's

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effects and argue that nicotine-containing tobacco products "stimulate the senses" and "calm[] feelings of stress," more like the effects of "hammocks [and] gardening tools" than those of products within FDA's jurisdiction.[13] The industry comments urge the Agency to follow the holding of *FTC v. Liggett & Myers Tobacco Co.*, 108 F. Supp. 573 (S.D.N.Y. 1952), *aff'd*, 203 F.2d 955 (1953), where the court concluded that the "soothing" effects of cigarettes do not affect the structure and function of the body.

FDA disagrees with these comments. As described earlier in this section, nicotine's effects on the structure and function of the body are comparable both in quality and quantity to those of tranquilizers, stimulants, weight control products, and products for long-term maintenance of addiction. These effects have long been recognized as effects on the structure or function of the body that are within FDA's jurisdiction. In addition, the Act's legislative history and case law interpreting the Act provide ample support for the conclusion that nicotine's effects are significant and within the scope of the Act. While "remote physical effect[s] on the body" may not be sufficient to invoke the Act's jurisdiction, *see Squibb*, 870 F.2d at 682, nicotine produces significant pharmacological and physiological effects on the structure and function of the body, and these effects clearly fall within sections 201(g)(1)(C) and 201(h)(3).

The courts have held that effects much less significant than those of nicotine are effects on the structure or function of the body and are within FDA's jurisdiction.

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[13] Joint Comments of the Smokeless Tobacco Manufacturers, Comment (Jan. 2, 1996), at 241. *See* AR (Vol. 526 Ref. 95).

Joint Comments of the Cigarette Manufacturers, Comment (Jan. 2, 1996), vol. II, at 65-66. *See* AR (Vol. 535 Ref. 96).

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Products whose effects have been found sufficient to fall within the scope of sections 201(g)(1)(c) and 201(h)(3) include those for temporary smoothing of wrinkles, *United States v. . . . "Line Away, Temporary Wrinkle Smoother,"* 284 F. Supp. 107 (D. Del. 1968), *aff'd*, 415 F.2d 369 (3d Cir. 1969); *United States v. . . . "Sudden Change,"* 409 F.2d 734 (2d Cir. 1969); and products that deliver low levels of oxygen for recreational use to enhance athletic performance, *United States v. . . . "Sports Oxygen,"* Civ. No. 89-2085 (D.N.J. Oct. 27, 1992), *reprinted in Federal Food, Drug, and Cosmetic Act: A Judicial Record, 1991-92*, 110-119. These effects are plainly less significant than the potent psychoactive, addictive, and weight-regulating effects of nicotine.

Weight loss is one of the effects of cigarettes and smokeless tobacco. *See* section II.A.4., below. Courts have held that this type of effect alone is sufficient to make cigarettes a drug when the product is "intended to affect the structure and functions of the human body by . . . achieving a reduction in the body's weight." *United States v. 354 Bulk Cartons . . . "Trim Reducing-Aid Cigarettes,"* 178 F. Supp. 847, 851 (D.N.J. 1959). Similarly, the legislative history of section 201(g)(1)(C) also demonstrates that weight loss alone is an effect on the structure and function of the body within the meaning of the Act. Indeed, one of the principal reasons cited by Congress for broadening the definition of "drug" to include products that affect the structure or function of the body was to bring weight control products within FDA's jurisdiction. *See* 78 Cong. Rec. 8960, 73d Cong., 2d Sess. (May 16, 1934) (statement of Senator Copeland), *reprinted in A Legislative History of the Federal Food, Drug, and Cosmetic Act and Its Amendments* (hereinafter Legislative History), vol. 2, at 831.

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The Agency disagrees that the effects of nicotine in cigarettes and smokeless tobacco are comparable to those produced by hammocks, gardening tools, or other similar articles. First, such articles do not introduce chemical ingredients into the body. By contrast, cigarettes and smokeless tobacco deliver a potent chemical ingredient, nicotine, whose significant pharmacological effects on the human body are widely recognized in the scientific community. Second, the powerful psychoactive effects produced by nicotine in cigarettes and smokeless tobacco are comparable to those produced by tranquilizers, stimulants, weight management agents, and drugs used for long-term maintenance of addiction, all of which are indisputably within FDA's jurisdiction. Third, as described in section I.A., above, tobacco industry officials have acknowledged that nicotine's effects are comparable to those of prescription drug products.

FDA also disagrees that the 1952 decision, *Liggett & Myers*, 108 F. Supp. 573, represents a controlling determination that cigarettes do not affect the structure or function of the body within the Act's meaning. Much less was known about the addictive, psychoactive, and weight-regulating effects of nicotine when the court decided *Liggett* in 1952 than is known today. The kinds of effects that were alleged in *Liggett* (lack of irritation to the respiratory system and "soothing" effects) are far different from the addicting and other psychoactive and weight-regulating effects now known to be caused by nicotine in cigarettes. *See* sections II.A.1. and IV., below. Moreover, *Liggett* was decided before FDA regulated nicotine. The Agency now regulates nicotine-containing products such as nicotine transdermal patches and nicotine nasal spray intended to treat nicotine addiction. If nicotine were not a powerful pharmacological agent with addictive

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properties; nicotine cessation products would be unnecessary. Further, the *Liggett* opinion does not suggest that the definition of "drug" would preclude treating cigarettes as drugs if new evidence concerning cigarettes' effects became known. *See* section IV., below.

Accordingly, FDA concludes that nicotine's significant pharmacological effects are effects on the structure or function of the body within the Act's meaning.

2. Tobacco industry comments contend that Congress intended to limit the drugs and devices covered by sections 201(g)(1)(C) and 201(h)(3) (products "intended to affect the structure or any function of the body") to products with "therapeutic" or "medical" uses. One industry comment further elaborates that the structure-function provision was added to the Federal Food, Drug, and Cosmetic Act in 1938 only as a result of concern that certain "therapeutic" products used for weight management purposes had escaped regulation under the 1906 Pure Food and Drug Act because obesity and leanness were not considered to be diseases. Consequently, this comment argues, the structure-function provision encompasses only products intended for "therapeutic" or "medical" use in "disease-treatment" conditions.[14]

This industry comment also makes a related argument that effects on the structure or function of the body must be "beneficial," or "drug-like," and not "destructive or toxic." According to this comment, "FDA views 'addictiveness' as an undesirable characteristic, not as a beneficial effect, and therefore more as a form of toxicity."[15] This

[14] Joint Comments of the Smokeless Tobacco Manufacturers, Comment (Jan. 2, 1996), at 145-146. *See* AR (Vol. 526 Ref. 95).

[15] *Id.* at 151.

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comment argues that the effects of cigarettes and smokeless tobacco are therefore outside the scope of the Act.

Conversely, one public interest group comment argues that construing sections 201(g)(1)(C) and 201(h)(3) as requiring a "therapeutic" effect would make these sections redundant of sections 201(g)(1)(B) and 201(h)(2), which define drugs and devices as products "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease." According to this comment, such an interpretation would violate basic rules of statutory construction.

The Agency disagrees with the tobacco industry's narrow reading of the structure-function provision. Neither the language of the statute, its legislative history, nor the case law supports the position that drugs and devices must have "therapeutic," "medical," or "beneficial" effects or purposes in order to "affect the structure or any function of the body."

The plain language of the statute provides no support for the tobacco industry's position. The terms, "therapeutic," "medical," and "beneficial," or words of similar import, do not appear anywhere in section 201(g)(1)(C) or 201(h)(3). FDA agrees with the comments that assert that construing the "structure or any function" language to require a therapeutic or medical effect would make these provisions essentially identical in scope and meaning to sections 201(g)(1)(B) and 201(h)(2). To do so would violate the well-accepted principle that "a legislature is presumed to have used no superfluous words." *Bailey v. United States*, 116 S.Ct. 501, 507 (1995).

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The legislative history is also inconsistent with the tobacco industry's position. Congress added sections 201(g)(1)(C) and 201(h)(3) to broaden the coverage of the Act to include a "comprehensive class of preparations which were intended to affect the structure or function of the body." "*Line Away*," 284 F. Supp. at 110 (citations omitted). The Act's legislative history makes clear that Congress intended to *expand* the Act's jurisdiction, rather than merely "close a loop-hole" in subsection 201(g)(1)(B). *See, e.g.*, H.R. Rep. No. 2139, 75th Cong., 3d Sess. 2 (1938), *reprinted in* 6 Legislative History 301 ("Drugs intended . . . for remedying underweight or overweight or for *otherwise* affecting bodily structure or function are subject to regulation") (emphasis added); *see also American Health Products Co. v. Hayes*, 574 F. Supp. 1498, 1506 (S.D.N.Y. 1983) (The structure-function provision was enacted to "reach those products . . . which evaded regulation altogether because they were neither foods *nor therapeutic agents*") (emphasis added).

The inclusive nature of the structure-function provision was raised several times during the hearings that led to enactment of the 1938 Act. *See Hearings on S. 1944, Senate Subcomm. of the Comm. on Commerce*, 73d Cong., 2d Sess. 15 (1933), *reprinted in* 1 Legislative History 107 ("The definition of the term 'drug' has been widened"); *Hearings on S. 2800, Senate Comm. on Commerce*, 73d Cong., 2d Sess. 516 (1934), *reprinted in* 2 Legislative History 519 ("This definition of 'drugs' is all-inclusive"); *Hearings on S. 5, Senate Comm. on Commerce*, 74th Cong., 1st Sess. 352 (1935), *reprinted in* 3 Legislative History 546 ("There is a universal recognition that the definition of the term 'drug' in the third subdivision is inclusive"). Congress consistently rejected

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suggestions to limit the drug definition to products with medical or medicinal purposes. *See, e.g., Hearings on S. 2800, Senate Comm. on Commerce*, 73d Cong., 2d Sess. 515-516 (1934), *reprinted in* 2 Legislative History 518-519.

Judicial decisions and Agency practice also conflict with the narrow interpretation urged by the manufacturers. As the Supreme Court has stated:

> Viewing the structure, the legislative history, and the remedial nature of the Act, . . . it [is] plain that Congress intended to define "drug" far more broadly than does the medical profession. . . .
>
> . . . the word "drug" is a term of art for the purposes of the Act, encompassing far more than the strict medical definition of that word. If Congress had intended to limit the statutory definition to the medical one, it could have so stated explicitly.

United States v. An Article of Drug . . . Bacto-Unidisk, 394 U.S. 784, 793 (1969).

The structure-function provision has been applied since 1938 to a wide assortment of products with a range of uses and effects, many of which cannot be considered "therapeutic." For example, products that have been found to be within this provision include those with cosmetic, recreational, economic, or other nontherapeutic purposes. These products include tanning booths; sunscreens; breast implants; injectable collagen; birth control pills; products purporting to remove wrinkles temporarily, *e.g.*, "*Line Away*," "*Sudden Change*"; products intended to eliminate pet odors, *e.g.*, *United States v. Undetermined Quantities . . .* "*Pets Smellfree*," 22 F.3d 235, 240 (10th Cir. 1994); products intended to grow hair, *e.g.*, *United States v. Kasz Enterprises, Inc.*, 855 F. Supp. 534, 540 (D.R.I.), *modified on other grounds*, 862 F. Supp. 717 (D.R.I. 1994); products intended as aphrodisiacs, *see* 54 FR 28780 (July 7, 1989), 21 CFR 310.528; products intended to enhance athletic performance by delivering a low, non-therapeutic level of

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oxygen, *e.g.*, "*Sports Oxygen*"; and veterinary products intended to increase milk production, *e.g.*, *United States v. Pro-Ag, Inc.*, 796 F. Supp. 1219 (D. Minn. 1991), *aff'd*, 968 F.2d 681 (8th Cir. 1992).

In the case of tanning booths, the Agency considers the product to be a "device" intended to affect the structure or any function of the body despite the fact that the American Academy of Dermatology considers tanning booths to be a potential health hazard and discourages their use.[16] FDA even regulates veterinary products intended to induce death in animals by humane means—an intended use that is indisputably not therapeutic. *See United States v. Articles of Drug . . . "Beuthanasia-D Regular,"* Civ. No. 77-0-396 (D. Neb. August 1, 1979), *reprinted in Federal Food, Drug, and Cosmetic Act: A Judicial Record, 1978-80*, 83-89.

The nature of a product's effect on the structure or function of the body—therapeutic or non-therapeutic, beneficial or adverse—thus does not determine FDA's jurisdiction. The relevant inquiry is simply whether a product has an effect on the structure or any function of the body. Cigarettes and smokeless tobacco do have such effects and, moreover, the effects are achieved through pharmacological means. The tobacco industry comments admit that products with "drug-type characteristics" (i.e., pharmacological action) are within the Act's jurisdiction.

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[16] Photobiology Task Force of the American Academy of Dermatology, Risks and benefits from high-intensity ultraviolet A sources used for cosmetic purposes: special report, *Journal of the American Academy of Dermatology* 1985;12:380-381. *See* AR (Vol. 711 Ref. 17).

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The argument that a product's effects must be therapeutic or medical is also inconsistent with FDA's assertion of jurisdiction over products with cosmetic, recreational, and economic uses. Notably, the comments that contend that effects on the structure or function of the body must be therapeutic or medical and also beneficial do not claim that FDA incorrectly applied the structure-function provision to products with cosmetic, recreational, or economic uses. Instead, these comments attempt to avoid the inconsistency between their arguments and these precedents by expansively interpreting "therapeutic" and "medical" to encompass products with cosmetic, recreational, economic, and other apparently non-therapeutic purposes or effects. Moreover, these comments do not provide any rationale to support the position that products regulating weight are subject to the Act, but that nicotine-containing cigarettes and smokeless tobacco, which also affect weight regulation, are not. Instead, the comments assert that the weight control effects of cigarettes and smokeless tobacco are too minor to be subject to the Act's jurisdiction. This argument is refuted in section II.A.4., below.

The Agency rejects the legal premise that effects on the structure or function of the body must be therapeutic or beneficial. However, even if the Agency were to accept the manufacturers' legal premise, this would not change the Agency's decision with respect to cigarettes and smokeless tobacco. As noted previously, cigarettes and smokeless tobacco produce pharmacological effects on the structure and function of the body that are indistinguishable from the effects of a wide range of products regulated by FDA, including sedation, stimulation, weight loss, and sustaining addiction. These pharmacological effects are as "therapeutic" or "beneficial" as many effects currently regulated under the

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Act, and would be sufficient to satisfy a requirement that products regulated as drug delivery devices have beneficial or therapeutic effects. Tobacco industry scientists have themselves argued that tobacco products provide "needed psychological benefits (increased mental alertness; anxiety reduction, coping with stress)"[17] and that "nicotine is a very remarkable beneficent drug."[18]

Indeed, if a new product with the powerful pharmacological effects of cigarettes and smokeless tobacco—sedation, stimulation, weight loss, and sustaining addiction—suddenly began to be distributed in the United States, there would be no question that the product would be subject to regulation under the Act because it "affect[s] the structure or any function of the body" within the Act's meaning. For example, the Agency has regulated gamma hydroxybutrate and gamma hydroxybutyric acid (collectively, GHB), a product intended to affect the structure or function of the body by promoting weight loss and muscle gain. The product is also used as a relaxant and sleep aid. GHB emerged as a steroid alternative after anabolic steroids became controlled substances. Very little was known about the product when GHB first entered the market because it was manufactured in clandestine laboratories (e.g., basements and kitchens), obtained from other black market sources, and usually distributed at health and sporting stores and clubs without labeling. The use of GHB as a steroid alternative and body-building aid is not "therapeutic"; nonetheless, the Agency successfully undertook regulatory actions against

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[17] Robinson JH, Pritchard WS. The role of nicotine in tobacco use, *Psychopharmacology* 1992;108:397-407, at 398. *See* AR (Vol. 66 Ref. 31-1).

[18] Ellis C. Science Advisor to the BATCO Board, *The Smoking and Health Problem*, presented at the BATCO Research Conference, Southampton, England (1962), at 15. *See* AR (Vol. 15 Ref. 190).

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GHB pursuant to the Act's drug authorities. *See United States v. Wood*, Nos. 92-50512, 92-50514 (9th Cir. Oct. 21, 1993); 58 FR 33690, 33699 (Jun. 18, 1993); FDA Quarterly Activities Report, First Quarter, FY 1991 (Oct.-Dec. 1990).

3. One comment contends that the structure-function provision is limited to products that "purport to *change* the physical structure of the body."[19] The Agency disagrees. Although the provision covers products that change a structure or function of the body, it is not limited to such effects. Courts have rejected the view that section 201(g)(1)(C) requires an actual "change [in] the physical structure or function of the [ ] body." "*Pets Smellfree,*" 22 F.3d at 237. Moreover, cigarettes and smokeless tobacco do in fact change the physical structure of the body by, for example, affecting brain chemistry and electrical activity in the brain, reducing weight, and increasing the growth of nicotine receptors in the central nervous system.

4. One comment asserts that the structure-function provision "is not intended to authorize the regulation of products solely because FDA believes their use is harmful and undesirable."[20] The Agency agrees. However, if a particular product meets the statutory definition of drug or device, the fact that it is also associated with harms to health is a reasonable consideration for the Agency in deciding to regulate the product. The Act's legislative history supports this view. As noted, concern about weight loss products that escaped regulation in the 1906 Pure Food and Drug Act was an impetus for

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[19] Joint Comments of the Cigarette Manufacturers, Comment (Jan. 2, 1996), vol. II, at 83 (emphasis added). *See* AR (Vol. 535 Ref. 96).

[20] Joint Comments of the Smokeless Tobacco Manufacturers, Comment (Jan. 2, 1996), at 152. *See* AR (Vol. 526 Ref. 95).

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broadening the definition of "drug" to include products that affect the structure or function of the body. Congress was concerned not so much with the weight-reduction effects of weight loss products but with the serious and undesirable harms to health that resulted from their use. *See, e.g., Hearing on H.R. 6906, H.R. 8805, H.R. 8941, and S. 5 Before a Subcomm. of the House Comm. on Interstate and Foreign Commerce*, 74th Cong., 1st Sess. 55 (1935) (statement of FDA Chief Walter Campbell), *reprinted in* 4 Legislative History 370.

5. Some comments state that FDA's determination that cigarettes and smokeless tobacco are "drugs" and "devices" would obligate the Agency to regulate caffeine and caffeine-containing products as drugs or drug delivery devices. These comments assert that for this reason the Agency should not regulate tobacco products as drugs or devices. The Agency disagrees that a comparison to caffeine provides a reason not to regulate nicotine-containing cigarettes and smokeless tobacco.

Caffeine is the active ingredient in several products regulated as drugs by the Agency. For instance, caffeine is the active ingredient in NoDoz, an over-the-counter stimulant that is regulated for its effects on the structure and function of the body. Caffeine is also an ingredient in internal analgesics and menstrual discomfort relief products.

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Although these products are regulated as drugs, the effects of these caffeine-containing products on the structure and function of the body are significantly less than those of nicotine. *See* section II.A.3.c.i., below. For instance, unlike nicotine, caffeine is not recognized at this time as an addictive drug by health organizations such as the

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American Psychiatric Association or the World Health Organization. Indeed, even an internal Philip Morris report comparing smoking and caffeine found that nicotine has a stronger stimulant effect than caffeine and that the stimulant effects of caffeine are "more like those of . . . placebo" than of nicotine.[21] The implication for nicotine-containing cigarettes and smokeless tobacco is clear: if caffeine in products such as NoDoz "affect[s] the structure or any function of the body within the meaning of the Act," then *a fortiori* nicotine-containing cigarettes and smokeless tobacco "affect the structure or any function of the body" as well.

Caffeine naturally occurs in coffee, tea, and other foods, and is used as an ingredient in soft drinks. The Act defines "food" as "articles used for food or drink for man or other animals." *See* section 201(f)(1) of the Act, 21 U.S.C. 321(f)(1). The statutory definition "includes articles used by people in the ordinary way most people use food—primarily for taste, aroma, or nutritive value." *Nutrilab v. Schweiker*, 713 F.2d 335, 338 (7th Cir. 1983). When caffeine is used in soft drink products in accordance with section 402 of the Act, 21 U.S.C. 342, and when it naturally occurs in other products that are foods, such as coffee, the product is a "food" under section 201(f)(1) of the Act, 21 U.S.C. 321(f)(1), and is explicitly excepted from the definition of drug in section 201(g)(1)(C), 21 U.S.C. 321(g)(1)(C) ("articles, *other than food*, intended to affect the structure or any function of the body") (emphasis added). The Agency's treatment of caffeine in beverages consequently has no bearing on how cigarettes and smokeless tobacco should be regulated.

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[21] Memorandum from Schori TR to Dunn WL, *Smoking and Caffeine: A Comparison of Physiological Arousal Effects* (May 17, 1972), at 1-2. *See* AR (Vol. 15 Ref. 189-7).

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6. Several comments assert that if FDA regulates nicotine-containing cigarettes and smokeless tobacco, it must also regulate the nicotine that occurs naturally in food products such as tomatoes, potatoes, eggplant, and cauliflower. The Agency disagrees. As noted above in response 5, section 201(g)(1)(C) specifically excludes from its coverage products that are "foods" under the Act. Tomatoes, potatoes, eggplant, and cauliflower are "foods" within the meaning of the Act because they are "articles used for food . . . for man." *See* section 201(f)(1), 21 U.S.C. 321(f)(1). While these vegetables do contain trace amounts of nicotine, a person would have to consume 206 pounds of tomatoes, 309 pounds of potatoes, 22 pounds of eggplant, or 355 pounds of cauliflower to obtain the same amount of nicotine as in one cigarette.[22] Thus, these products are appropriately regulated as foods.

7. Some comments question whether applying the structure-function provision to nicotine-containing cigarettes and smokeless tobacco might provide precedent for applying the provision to a wide range of products that have effects on the structure or function of the body—including guns and other weapons, products that prevent injury, such as airbags, and chemical sprays used for self-defense or law enforcement purposes.

The Agency has never construed the structure-function provision to include products such as guns, airbags, and chemical sprays, and applying the structure-function provision to nicotine-delivering tobacco products will not provide any precedent for doing

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[22] Chart Y, prepared in conjunction with the testimony of David Kessler before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives (Mar. 25, 1994). *See* AR (Vol. 296 Ref. 4175).

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so. Moreover, there are fundamental distinctions between these products and nicotine-delivering tobacco products. Cigarettes deliver a pharmacologically active dose of the drug nicotine to the body through inhalation. Smokeless tobacco delivers a pharmacologically active dose of the same drug through buccal absorption. Collectively, tobacco products achieve their effects on the structure and function of the body through nicotine's pharmacological effects. These include sedation, stimulation, weight control, and maintenance of addiction. Tobacco products are thus indistinguishable from products that the Agency has traditionally regulated as drugs and devices. In contrast, guns, airbags, and chemical sprays are markedly different and distinguishable from such products.

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II. CIGARETTES AND SMOKELESS TOBACCO ARE "INTENDED" TO AFFECT THE STRUCTURE AND FUNCTION OF THE BODY WITHIN THE MEANING OF THE ACT

Cigarettes and smokeless tobacco clearly "affect the structure or any function of the body." The principal issue before the Food and Drug Administration (FDA) is thus whether these effects are "intended" within the meaning of the Federal Food, Drug, and Cosmetic Act (the Act).

The Act's drug and device definitions provide in pertinent part that an article is a drug or device if it is "*intended* to affect the structure or any function of the body." Sections 201(g)(1)(C) and 201(h)(3), 21 U.S.C. 321(g)(1)(C) and (h)(3) (emphasis added). In determining whether an article is "intended" to affect the structure or function of the body, "the FDA is not bound by the manufacturer's subjective claims of intent," but rather can find actual intent "on the basis of objective evidence." *National Nutritional Foods Ass'n (NNFA) v. Mathews*, 557 F.2d 325, 334 (2d Cir. 1977). That is, the Agency determines the intent of the manufacturers objectively by evaluating all of the relevant evidence in the record from the perspective of a reasonable fact finder. *See* 21 CFR 201.128, 801.4. In determining intended use, the Agency may "examine a wide range of evidence." *United States v. Two Plastic Drums . . . Black Currant Oil*, 761 F. Supp. 70, 72 (C. D. Ill. 1991), *aff'd*, 984 F.2d 814 (7th Cir. 1993).

In the Jurisdictional Analysis, 60 FR 41453–41787, the Agency determined, based on the evidence then available to it, that cigarettes and smokeless tobacco are "intended" to affect the structure and function of the body. This determination was based on three grounds:

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(1) The addictive, psychoactive, and other significant pharmacological effects of cigarettes and smokeless tobacco are so widely known and foreseeable that these effects may be deemed to have been intended by the manufacturers, *see* Jurisdictional Analysis, 60 FR 41483–41490;

(2) Such a large percentage of consumers use cigarettes and smokeless tobacco to satisfy their addiction or to obtain other pharmacological effects that the manufacturers may be deemed to intend that their products will be used for such purposes, *see* Jurisdictional Analysis, 60 FR 41490–41491; and

(3) The statements, research, and actions of the tobacco manufacturers show that the manufacturers actually intend their products to affect the structure or any function of the body, *see* Jurisdictional Analysis, 60 FR 41491–41520.

FDA received comments on its findings from the tobacco industry, public health organizations, and other interest groups and members of the public.

In this section, the Agency considers, in light of the public comments, the objective evidence in the administrative record relevant to whether cigarette and smokeless tobacco manufacturers intend their products to affect the structure or any function of the body, including new evidence that has become available since the issuance of the Jurisdictional Analysis. The Agency also discusses the legal standard for establishing the intended use of cigarettes and smokeless tobacco, and responds to the substantive comments received by the Agency on the evidence and the legal standard. Specifically:

- Section II.A. discusses the evidence supporting FDA's finding that it is foreseeable to a reasonable tobacco manufacturer that the nicotine in cigarettes and smokeless tobacco will cause pharmacological effects and will be used by consumers for those effects and responds to comments on this issue:

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- Section II.B. discusses the evidence supporting FDA's finding that consumers use cigarettes and smokeless tobacco predominantly to obtain the pharmacological effects of nicotine and responds to comments on this issue;
- Section II.C. discusses the evidence supporting FDA's finding that cigarette manufacturers' statements, research, and actions show that they intend their products to be used for the pharmacological effects of nicotine and responds to comments on this issue;
- Section II.D. discusses the evidence supporting FDA's finding that smokeless tobacco manufacturers' statements, research, and actions show that they intend their products to be used for the pharmacological effects of nicotine and responds to comments on this issue;
- Sections II.E. and F. respond to comments, not already addressed in the foregoing sections, on the legal standard for evaluating intended use; and
- Section II.G. discusses the cumulative evidence of intended use.

Except as modified below, FDA confirms its prior findings and incorporates them by reference. FDA concludes that the evidence on the foreseeability of nicotine's effects, actual consumer use of tobacco for those effects, and evidence of intended use based on industry statements, research, and actions each provides an independent basis for the determination that the manufacturers of cigarettes and smokeless tobacco intend their products to affect the structure of function of the body.

Although the evidence thus provides several independent bases for establishing that cigarettes and smokeless tobacco are intended to affect the structure and function of the body, the Agency also looks at the objective evidence of intent as a whole. The

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Agency finds that, both independently and cumulatively, the evidence of foreseeable pharmacological effects and uses, actual consumer use for pharmacological purposes, and manufacturer intent as revealed through the statements, research, and actions of the manufacturers convincingly supports the Agency's determination that cigarettes and smokeless tobacco are intended to affect the structure and function of the body.

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A. A REASONABLE MANUFACTURER WOULD FORESEE THAT CIGARETTES AND SMOKELESS TOBACCO WILL CAUSE ADDICTION AND OTHER PHARMACOLOGICAL EFFECTS AND WILL BE USED BY CONSUMERS FOR PHARMACOLOGICAL PURPOSES

FDA may conclude that a product is intended to affect the structure or function of the body if a reasonable person in the position of the manufacturer would foresee that the product will have pharmacological effects and that a substantial proportion of consumers will use the product for those effects. In the Jurisdictional Analysis, the Agency made extensive findings, based on the evidence then available, regarding the pharmacological effects of tobacco on the human body. *See* Jurisdictional Analysis, 60 FR 41534–41575. FDA received comments on these findings from the tobacco industry, many medical and public health organizations and medical practitioners, and from other members of the public. The administrative record includes extensive, publicly disseminated evidence from scientific studies and expert panels on the subject of tobacco's pharmacological effects on the human body.

After considering the administrative record and reviewing public comments, the Agency finds that the evidence clearly demonstrates that a reasonable tobacco manufacturer would foresee that cigarettes and smokeless tobacco will cause and sustain addiction, produce other psychoactive effects, and control weight and be used by consumers for these effects. This finding provides an independent basis for the Agency's conclusion that cigarettes and smokeless tobacco are intended to affect the structure and function of the body.

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In section II.A.1., below, FDA describes the legal basis for considering evidence of the foreseeable effects and uses of a product. FDA presents its major findings and responds to significant comments in sections II.A.2. through II.A.6. In section II.A.7., FDA responds to the remaining relevant substantive comments.

1. "Intended Use" May Be Established on the Basis of Foreseeable Pharmacological Effects and Uses

The Agency's legal authority to establish intended use based on the foreseeable effects and the foreseeable uses of a product comes from the plain language of the Act, as well as from FDA's regulations, case law, administrative precedent, and the public health purposes of the Act.

The plain language of the Act provides that a drug or device is an article "*intended* to affect the structure or any function of the body." Sections 201(g)(1)(c) and 201(h)(3) of the Act, 21 U.S.C. 321(g)(1)(C), 321(h)(3) (emphasis added). It is a widely accepted legal principle that persons can be held to "intend" the reasonably foreseeable consequences of their actions. In 1938, when Congress defined drugs and devices as articles "intended" to affect the structure or any function of the body of man, it was well established that "[t]he law presumes that every man *intends* the legitimate consequences of his own acts." *Agnew v. United States*, 165 U.S. 36, 53 (1897); *accord Fanning v. United States*, 72 F.2d 929, 932 (4th Cir. 1934) ("the law imputes an intent to accomplish the natural results of one's own act") (citations omitted); *Eastern Drug Co. v. Bieringer-Hanauer Co.*, 8 F.2d 838, 839 (1st Cir. 1925) ("presumption that one intends the natural and probable consequences of his acts"); *see also* 4 *Wigmore on Evidence* 3388-3390

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(1904-1905) (intent is "a volition having consequences which ought reasonably to have been foreseen"), *quoted in Rushmore v. Saxon*, 158 F. 499, 506 (C.C.S.D.N.Y. 1908).

In accordance with this well-accepted legal principle, FDA may establish that a manufacturer "intends" that its product affect the structure or function of the body when it is foreseeable that the product will in fact affect the structure or function of the body in a drug-like manner. The case for establishing intent through foreseeability is especially strong when a reasonable manufacturer would foresee that a product will *both* act like a drug *and* be commonly used like a drug. Where it is foreseeable that a product will have pharmacological effects on a significant proportion of consumers and will be used by these consumers to obtain these pharmacological effects, the statute allows FDA to recognize reality and find that the manufacturer "intends" its product to be used as a drug.

Consistent with this well-established understanding of "intent," FDA's regulations defining "intended use" contemplate that foreseeability can be a basis for establishing the objective intent of the manufacturer. These regulations require product labeling to include adequate directions for all "intended uses." 21 CFR 201.5 (drugs); 21 CFR 801.5 (devices). The intended uses of a drug or device that must be included on the label are defined to include those that are, or that reasonably can be, anticipated by the manufacturer.

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The definition of "intended uses" for drugs establishes an "objective intent" standard. Specifically, the regulations provides:

> The words "intended use" or words of similar import . . . refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example,

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> be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the drug, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. But *if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it*, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.

21 CFR 201.128 (emphasis added). The definition of "intended uses" for devices is essentially identical. 21 CFR 801.4. Thus, under these regulatory provisions, objective intent can be established by evidence showing that the manufacturer "knows" or "has knowledge of facts that would give him notice," i.e., that a reasonable manufacturer would foresee that consumers will use a product for drug or device uses.[23]

Other parts of the regulations also provide that foreseeable pharmacological uses should be considered to be intended by the manufacturer. Section 201.128, for instance,

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[23] The Agency disagrees with the tobacco industry's suggestion that this foreseeability test must be interpreted to apply only to products that are already classified as "drugs" or "devices." The Agency regularly uses the regulatory definition of "intended uses" to determine whether products should be classified as drugs or devices. *See, e.g., United States v. Articles of Drug*, 625 F.2d 665, 668 n.5 (5th Cir. 1980); *United States v. Undetermined Quantities of An Article or Drug Labeled as "Exachol,"* 716 F. Supp. 787, 791 (S.D.N.Y. 1989); *United States v. 22 . . . devices . . . "The Ster-o-lizer MD-200,"* 714 F. Supp. 1159, 1165 (D. Utah 1989); *United States v. Kasz Enterprises*, 855 F. Supp. 534, 539 (D.R.I. 1994), modified on other grounds, 862 F. Supp. 717 (D.R.I. 1994); *United States v. Articles of Food and Drug Consisting of . . . Apricots*, 444 F. Supp. 266, 273 (E.D. Wis. 1977). Thus, the Agency relies on the test of objective intent in the regulation (including the foreseeability standard described above) to establish: (1) in the case of products already classified as drugs or devices, the intended uses that must appear on the product labeling; and (2) in the case of products not yet classified as drugs or devices, the intended uses that determine whether the product should be classified as a drug or device. The Agency's interpretation of its own regulation is reasonable and entitled to "controlling weight." *Thomas Jefferson Univ.* 114 S. Ct. 2381, 2386 (1994).

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further provides that "objective intent . . . may be shown by the circumstance that the article is, *with the knowledge of such persons* or their representatives, *offered and used for a purpose for which it is neither labeled nor advertised.*"[24] 21 CFR 201.128 (emphasis added).

The case law and administrative precedent interpreting the Act recognize that the foreseeable pharmacological effects and uses of a product are proper grounds for establishing intent. These precedents recognize that the Agency may consider evidence of the likely consumer use of a product in determining intended use. *See, e.g., Two Plastic Drums*, 761 F. Supp. at 72; *Kasz*, 855 F. Supp. at 539. They also recognize that a foreseeable drug effect is generally persuasive evidence that the product is intended to affect the structure and function of the body. For example, the court in *United States v. Undetermined Quantities . . . "Pets Smellfree"* found that the presence of chlortetracycline, a drug ingredient, at doses sufficient to reduce the level of bacteria in animal intestines was evidence that the product was intended to affect the structure and function of the body. 22 F.3d 235, 240 (10th Cir. 1994).[25] Indeed, the court found this evidence to be relevent even though the dose of chlortetracycline in the product was "subtherapeutic"—that is, the dose was sufficient to reduce bacteria levels, but not to cure

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[24] The tobacco industry contends that the requirement that the product must be "offered" as well as used for an unlabeled or unadvertised use means that there must be a specific marketing representation promoting the use. The Agency does not so interpret the regulation. The ordinary definition of the word "offer" means simply "[t]o present for acceptance or rejection." *American Heritage Dictionary of the English Language* (3d ed. 1992) at 1255. Moreover, the tobacco industry's interpretation conflicts with the language in the regulation that provides that the use for which the product is offered is a use "for which it is neither labeled nor advertised." Consistent with the language of the regulation, the Agency interprets the requirement that the product be "offered" to mean simply that the product be presented to the consumer for purchase.

[25] *See* section II.E., below, for an additional discussion of the relevant case law and administrative precedent.

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or treat a disease. *Id.* Administratively, the Agency has asserted jurisdiction over products such as khat, imitation cocaine, hormone-containing skin creams, and fluoride-containing toothpastes based primarily, if not exclusively, on evidence that these products have foreseeable drug effects and drug uses. *See* section II.E.1.e., below.

Cases interpreting other public health statutes establish a test for determining intended use that is the same as the one used by FDA and that permits reliance on foreseeable uses. In *N. Jonas & Co. v. EPA*, 666 F.2d 829 (3d Cir. 1981), for example, the court held that a product was "intended for use" as a pesticide under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) based on its foreseeable consumer use—even though the manufacturer did not promote the product as a pesticide (and even disclaimed use as a pesticide on the label). The court stated:

> The Act [and] the regulations . . . focus inquiry on the intended use, implicit or expressed. *We take this to mean the use which a reasonable consumer would undertake . . . . In determining intent objectively, the inquiry cannot be restricted to a product's label and to the producer's representations. Industry claims and general public knowledge can make a product pesticidal notwithstanding the lack of express pesticidal claims by the producer itself.*

Id. at 833 (emphasis added).

Similarly, in *United States v. Focht*, 882 F.2d 55, 60 (3d Cir. 1989), the court held that under the Federal Hazardous Substances Act (FHSA), "[i]ntended use . . . , objectively defined, necessarily encompasses foreseeability." In this case, the Consumer Product Safety Commission sought to take action against fireworks components that could be assembled to make banned fireworks. The court found that the testimony that 90% of consumers who order the components will use the components to make illegal fireworks "makes it foreseeable that the components in question will be used to build

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banned fireworks. Such knowledge must be attributed to [the defendants]." *Id.*; *accord United States v. Articles of Banned Hazardous Substances . . . Baby Rattles*, 614 F. Supp. 226 (E.D.N.Y. 1985).

The tobacco industry argues that the Agency may not rely on the interpretation of "intended use" in other statutes to interpret "intended use" under the Federal Food, Drug, and Cosmetic Act. The fact that FDA's interpretation of "intended use" under the Federal Food, Drug, and Cosmetic Act parallels the interpretation under other public health statutes, however, strongly supports the reasonableness of the Agency's analysis. Indeed, the court in *Jonas* relied in part on cases interpreting intended use under the Federal Food, Drug, and Cosmetic Act in holding that intended uses encompass readily foreseeable consumer uses, specifically citing *National Nutritional Foods Ass'n (NNFA) v. Mathews*, 557 F.2d 325, 334 (2d Cir. 1977), for the proposition that "FDA [is] not bound by manufacturer's subjective claims of intent in assessing whether product is intended as a drug," and *Bacto-Unidisk*, 394 U.S. 784 (1969), for the proposition that "the definition of drug [is] to be given liberal interpretation in light of remedial purpose of Federal Food, Drug and Cosmetic Act." 666 F.2d at 833.[26]

Moreover, contrary to the tobacco industry's contention, the FHSA and FIFRA cannot be distinguished from the Federal Food, Drug, and Cosmetic Act on the ground that foreseeability principles are alien to the Federal Food, Drug, and Cosmetic Act. Several other provisions of the Act contemplate foreseeability principles. *See, e.g.*, 21

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[26] Similarly, courts interpreting the Federal Food, Drug, and Cosmetic Act rely on interpretations of analogous consumer protection statutes. *See, e.g.*, *"Sudden Change,"* 409 F.2d 734, 741 n.8 (2d Cir. 1969) (citing a case interpreting the Federal Trade Commission Act because "the remedial purpose of the Federal Trade Commission Act is sufficiently analogous").

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U.S.C. 321(n) (an article may be misbranded if its labeling and advertising fail to reveal "consequences which may result from . . . such conditions of use as are customary or usual"); 21 U.S.C. 360h (FDA authorized to recall devices that "present[] an unreasonable risk of substantial harm").

Indeed, in *United States v. Park*, 421 U.S. 658 (1975), the Supreme Court concluded that the Federal Food, Drug, and Cosmetic Act imposes "requirements of foresight and vigilance" on manufacturers, stating:

> the Act imposes not only a positive duty to seek out and remedy violations when they occur but also, and primarily, a duty to implement measures that will insure that violations will not occur. The requirements of *foresight and vigilance* imposed on responsible corporate officials are beyond question demanding, and perhaps onerous, but they are no more stringent than the public has a right to expect of those who voluntarily assume positions of authority in business enterprises whose services and products affect the health and well-being of the public that supports them.

Id. at 672 (emphasis added).

Compelling policy reasons support the Agency's interpretation that it may establish that a product is intended to affect the structure or function of the body when it is foreseeable that a product will produce significant pharmacological effects in consumers and be widely used by consumers for these effects. The manufacturers' position is that they may ignore overwhelming scientific evidence that their product will have and be used for pharmacological effects so long as they avoid promoting their product for these pharmacological effects. Under this interpretation, however, the manufacturer of virtually any drug or device could avoid regulation under the Act—no matter how substantial and well-established the pharmacological effects and uses of the product—by simply avoiding making certain claims in the product's labeling and advertising. For example, it is not

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difficult to imagine a manufacturer of a generic version of a drug like Prozac (fluoxetine hydrochloride), an antidepressant drug currently available only by prescription, seeking to avoid FDA regulation by advertising its product as intended solely for the "pleasure" of its consumers. *See* section II.F.1.e., below.

Accepting the manufacturers' position would leave the public vulnerable to the unregulated distribution of products with known pharmacologically active ingredients. Moreover, it would reward manufacturers who deny the obvious pharmacological effects and uses of their products in their public statements, labeling, and advertising. Thus, the Agency concludes that the public health objectives of the Act require the Agency to regulate as "drugs" or "devices" products that can be foreseen to have widespread pharmacological effects and uses.

2. The Significant Pharmacological Effects and Uses of Cigarettes and Smokeless Tobacco Are Foreseeable

The evidence in the administrative record establishes that the pharmacological effects and uses of cigarettes and smokeless tobacco are so widespread and well-known that a reasonable manufacturer would foresee them. Since the Agency last considered the issue of whether cigarettes are drugs over 15 years ago, a scientific consensus has emerged that nicotine is addictive and has other significant pharmacological effects.

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Nicotine—the essential ingredient in cigarettes and smokeless tobacco—is a pharmacological agent that substantially alters the structure and function of the brain and other systems of the body. After a single puff inhaled from a cigarette, nicotine enters the mouth, passes into the lungs, is absorbed from the lungs into the bloodstream, and diffuses

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from the blood into the brain. This process takes about 11 seconds.[27] When consumed in smokeless tobacco, nicotine is absorbed through the lining of the mouth into the bloodstream and flows to the brain.

Once inside the human brain, nicotine binds to unique receptors on the surfaces of brain cells. These nicotinic receptors normally interact with a natural chemical messenger called acetylcholine, but can also be stimulated by nicotine to alter mood, alertness, and cognition. Exposure to nicotine causes the number of nicotinic receptors on the surfaces of brain cells to increase[28] and significantly alters the brain's normal electrical and metabolic activity.[29] Nicotine's actions on the central nervous system produce both

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[27] Department of Health and Human Services, Office on Smoking and Health, *The Health Consequences of Smoking: Nicotine Addiction, a Report of the Surgeon General* (Jul. 29, 1988), DHHS Publication No. (CDC) 88-8406 (Washington DC: GPO, 1988), at 13-14 (hereinafter cited as Surgeon General's Report, 1988). *See* AR (Vol. 129 Ref. 1592).

Benowitz NL, *Clinical Pharmacology of Inhaled Drugs of Abuse: Implications in Understanding Nicotine Dependence*. NIDA Research Monograph 99 (Rockville MD: National Institute on Drug Abuse, 1990), at 17. *See* AR (Vol. 3 Ref. 18).

[28] Benwell MEM, Balfour DJK, Anderson JM, Evidence that tobacco smoking increases the density of (−)-[^{3}H]nicotine binding sites in human brain, *Journal of Neurochemistry* 1988;50:1243-1247. *See* AR (Vol. 136 Ref. 1570).

[29] Surgeon General's Report, 1988, at 79-123. *See* AR (Vol. 129 Ref. 1592).

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sedating and stimulating effects, depending on dose and circumstances.[30] Nicotine also plays a role in weight regulation.[31]

In addition to its sedating and stimulating effects, nicotine causes and sustains addiction. Nicotine directly affects an intrinsic brain system, known as the mesolimbic system, that signals pleasure and reward and modulates emotions. When stimulated by an addictive substance, the mesolimbic system responds by rewarding the repeated consumption of the substance.[32] It is widely believed that amphetamine, cocaine, and nicotine all cause the compulsive drug-seeking behavior of drug addiction through the same mechanism: increasing the activity of the neurotransmitter dopamine within the mesolimbic system.[33]

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[30] Pritchard WS, Gilbert DG, Duke DW, Flexible effects of quantified cigarette-smoke delivery on EEG dimensional complexity, *Psychopharmacology* 1993;113:95-102. *See* AR (Vol. 3 Ref. 23-1).

Pritchard WS, Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490. *See* AR (Vol. 105 Ref. 965).

Norton R, Brown K, Howard R, Smoking, nicotine dose and the lateralisation of electrocortical activity, *Psychopharmacology* 1992;108:473-479. *See* AR (Vol. 3 Ref. 22).

Golding JF, Effects of cigarette smoking on resting EEG, visual evoked potentials and photic driving, *Pharmacology, Biochemistry and Behavior* 1988;29:23-32. *See* AR (Vol. 3 Ref. 23-3).

[31] Surgeon General's Report, 1988, at 431-432. *See* AR (Vol. 129 Ref. 1592).

[32] Pomerleau OF, Pomerleau CS, Neuroregulators and the reinforcement of smoking: towards a biobehavioral explanation, *Neuroscience and Biobehavioral Reviews* 1984;8:503-513. *See* AR (Vol. 3 Ref. 20-1).

Wise RA, Rompre PP, Brain dopamine and reward, *Annual Review of Psychology* 1989;40:191-225. *See* AR (Vol. 3 Ref. 19-1).

Clarke PBS, Mesolimbic dopamine activation—the key to nicotine reinforcement? *CIBA Foundation Symposium* 1990;152:153-168. *See* AR (Vol. 3 Ref. 19-2).

[33] *Id.*

Pontieri FE, Tanda G, Orzi F, *et al.*, Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs, *Nature* 1996;382:255-257. *See* AR (Vol. 711 Ref. 51).

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Extensive scientific evidence demonstrating the significant effects of nicotine in tobacco products on the structure and function of the body is discussed in detail in the remainder of this section. The magnitude and wide dissemination of the scientific evidence demonstrates that it is foreseeable to a reasonable person in the position of tobacco manufacturer that many consumers will use tobacco products for these pharmacological effects.

3. Nicotine Is Widely Recognized as Addictive, and It Is Foreseeable That Consumers Will Use Cigarettes and Smokeless Tobacco To Satisfy an Addiction

Nicotine's effects on the brain are the biological basis of nicotine addiction—an addiction that has been proven by a wealth of laboratory and epidemiological evidence and recognized by every major independent medical organization that has studied the question. Nicotine's widely recognized addictive properties make it foreseeable to any reasonable person that a substantial proportion of users of tobacco products will consume these products to satisfy their addiction.[34]

a. Scientific Consensus

Overwhelming scientific evidence and broad recognition that nicotine is an

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Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Sciences of the United States of America* 1988;85:5274-5278. *See* AR (Vol. 66 Ref. 26).

Corrigall WA, Franklin KBJ, Coen KM, *et al.*, The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. *Psychopharmacology* 1992;107:285-289. *See* AR (Vol. 8 Ref. 93-4).

[34] FDA's conclusion that the pharmacological effects and uses of nicotine in cigarettes and smokeless tobacco are foreseeable rests on published literature, including widely disseminated government reports. FDA's conclusion that the tobacco industry knows that nicotine has substantial pharmacological effects and that consumers use tobacco for these effects, *see* section II.C., below, is based largely on internal company documents.

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addictive, dependence-producing substance emerged in the 1980's.[35] All leading expert and public health organizations in the United States and the international community with expertise in tobacco or drug addiction now recognize that nicotine is addictive. The first major organization to do so was the American Psychiatric Association in 1980, when its *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III), defined the Tobacco Dependence Disorder and the Tobacco Withdrawal Syndrome.[36] Since 1980, nicotine in tobacco products has also been recognized as addictive by the U.S. Surgeon General (1986 and 1988)[37] American Psychological Association (1988),[38] the Royal Society of Canada (1989),[39] the World Health Organization (WHO) (1992),[40] the

[35] The terms "addictive" and "dependence-producing" are used interchangeably among experts and scientific organizations and generally refer to the persistent and repetitive intake of a psychoactive substance despite evidence of harm and a desire to quit. In this document, FDA also uses both terms interchangeably. The term "abuse liability" also refers to a substance's ability to produce dependence or addiction.

[36] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 3d ed. (Washington DC: American Psychiatric Association, 1987), at 159-160, 176-178. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[37] Department of Health and Human Services, Office on Smoking and Health, The Health Consequences of Using Smokeless Tobacco, A Report of the Advisory Committee to the Surgeon General (Apr. 1986). NIH Publication No. 86-2874 (Bethesda, MD:1986). *See* AR (Vol. 128 Ref. 1591)

Surgeon General's Report, 1988. *See* AR (Vol. 129 Ref. 1592).

[38] *Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce*, U.S. House of Representatives, 100th Cong., 1st Sess. 1 (Jul. 29, 1988) (statement of the American Psychological Association). *See* AR (Vol. 5 Ref. 43-5).

[39] Royal Society of Canada, *Tobacco, Nicotine, and Addiction: A Committee Report*, prepared at the request of the Royal Society of Canada for the Health Protection Branch, Health and Welfare Canada (Aug. 31, 1989), at v-vi. *See* AR (Vol. 62 Ref. 814).

[40] WHO, *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines* (Geneva: World Health Organization, 1992), at 76. *See* AR (Vol. 43 Ref. 175).

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American Medical Association (1993),[41] and the Medical Research Council in the United Kingdom (1994).[42] Every expert organization that has commented on whether nicotine is addictive has concluded that it is.

Recognition of nicotine addiction is now so universal that even the vast majority of scientists who have received funding from the tobacco industry believe that nicotine is addictive. In a survey of principal investigators of research projects funded by the tobacco industry in 1989, 83.3% agreed strongly and an additional 15.3% agreed somewhat that cigarette smoking is addictive.[43] Moreover, as demonstrated in section II.C., below, the tobacco industry itself, despite public pronouncements to the contrary, has long known nicotine to be addictive.

Salient findings that reflect nicotine's addictiveness include the following:

Epidemiological Evidence.

- Persons who have smoked at least one cigarette are about twice as likely to develop dependence as are persons who have ever tried cocaine or alcohol.[44]

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[41] American Medical Association. Ethyl alcohol and nicotine as addictive drugs, in *1993 AMA Policy Compendium* (Chicago: AMA, 1993), at 35. *See* AR (Vol. 37 Ref. 2).

[42] Medical Research Council. *The Basis of Drug Dependence*. MRC Field Review (London: Medical Research Council, 1994), at 11. *See* AR (Vol. 41 Ref. 105).

[43] Cummings KM, Sciandra R, Gingrass A, *et al.*, What scientists funded by the tobacco industry believe about the hazards of cigarette smoking, *American Journal of Public Health*, 1991;81(7):894-896. *See* AR (Vol. 5 Ref. 44).

[44] Anthony JC, Warner LA, Kessler RC, Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from the National Comorbidity Survey, *Experimental and Clinical Psychopharmacology* 1994;2:244-268. *See* AR (Vol. 37 Ref. 4).

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- More than half of people presenting for treatment of alcohol or drug abuse who also smoke cigarettes report that quitting smoking would be harder than giving up their other drug of abuse.[45]
- Despite the interest of 70% of smokers in quitting smoking, fewer than 3% succeed per year.[46]
- About two of every five users of smokeless tobacco have attempted to quit and failed,[47] and 68% of smokeless tobacco users who have attempted to quit report an average of four such attempts.[48]
- About 50% of smokers recovering from surgery for a smoking-related disease (e.g., lung cancer) and whose prognosis and symptoms would be improved by abstinence resume smoking.[49]

Evidence from Animal and Human Laboratory Studies.

- Nicotine has been determined to have significant potential to produce addiction in humans on the basis of the same screening tests used to evaluate the addictive potential of any drug by the World Health Organization, the Drug Enforcement Administration,

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[45] Kozlowski LT, Wilkinson A, Skinner W, *et al.*, Comparing tobacco cigarette dependence with other drug dependencies, *Journal of the American Medical Association* 1989;261(6):898-901. *See* AR (Vol. 41 Ref. 92).

[46] Centers for Disease Control and Prevention, Cigarette smoking among adults—United States, 1993, *Morbidity and Mortality Weekly Report* 1994 (Dec. 23);43:925-930. *See* AR (Vol. 36 Ref. 616-1).

[47] Novotny TE, Pierce JP, Fiore MC, *et al.*, Smokeless tobacco use in the United States: the adult use of tobacco surveys, *Monographs/National Cancer Institute* 1989:8:25-28. *See* AR (Vol. 41 Ref. 109).

[48] Severson HH, Enough snuff: ST cessation from the behavioral, clinical, and public health perspectives, in *Smokeless Tobacco or Health, An International Perspective*, Smoking and Tobacco Control Monograph 2, NIH Publication No. 93-3461 (Washington DC: DHHS, 1993), at 281-282. *See* AR (Vol. 18 Ref. 5-1).

[49] Surgeon General's Report, 1988, at 150. *See* AR (Vol. 129 Ref. 1592).

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the National Institute on Drug Abuse (NIDA), the College on Problems of Drug Dependence, pharmaceutical companies, and FDA's Drug Abuse Advisory Committee (the Committee).[50] *See* section II.A.3.c.i., below.

- Nicotine's effects in the brain have been shown to be critical in the self-administration of nicotine by both animals and humans.[51] (The tendency of a substance to be self-administered demonstrates its ability to cause an animal or human to seek repeated doses of the substance.) This finding is a key element of addiction.
- The ability of nicotine to produce strong physiological and behavioral effects, including death at high doses, is no less than that of amphetamine or morphine.[52]

Other Biological Evidence.

- Nicotine increases dopamine activity in the mesolimbic system of the brain. As with cocaine, amphetamine, and other drugs, this effect is believed to contribute to the compulsive drug-seeking behavior of addiction.[53]
- Chronic nicotine exposure causes the number of nicotinic receptors on the surfaces of brain cells to increase. This phenomenon is associated with tolerance to the effects of nicotine and has been well documented in animals and people.[54]

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[50] *Id.* at 270.

[51] *Id.* at 166, 173-175, 182-192.

Corrigall WA, Coen KM. Nicotine maintains robust self-administration in rats on a limited access schedule. *Psychopharmacology* 1989;99:473-478. *See* AR (Vol. 136 Ref. 1561).

[52] Surgeon General's Report. 1988, at 272-274, 594. *See* AR (Vol. 129 Ref. 1592).

[53] Corrigall WA, Franklin KBJ, Coen KM, *et al.*, The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. *Psychopharmacology* 1992;107:285-289. *See* AR (Vol. 8 Ref. 93-4).

[54] Marks MJ, Burch JB, Collins AC, Effects of chronic nicotine infusion on tolerance development and nicotine receptors, *Journal of Pharmacology and Experimental Therapeutics* 1983;226:817-825. *See* AR (Vol. 41 Ref. 103).

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Commercial Evidence.

- Non–nicotine-containing tobacco products have never proved successful substitutes for tobacco despite the sophistication of some of them (e.g., Philip Morris' Next) in mimicking the non–nicotine-mediated effects of conventional cigarettes.

These data are just a few selections from the overwhelming evidence that has led the world's health authorities to classify nicotine as addictive. The following sections describe in detail the definition of addiction and how the widely known scientific evidence would lead any reasonable manufacturer to foresee that a significant proportion of tobacco consumers will become addicted to nicotine and will use tobacco products to satisfy their addiction.

b. Definition of Addiction

The tobacco industry is virtually alone in publicly contending that nicotine is not addictive. Its primary argument for rejecting the massive body of research and the expert opinion of every authoritative medical organization that has considered the issue is to claim that the entire scientific community is using the wrong definition of addiction.[55] According to the tobacco industry, the "traditional criteria" of addiction are "meaningful

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Surgeon General's Report, 1988, at 53-54. *See* AR (Vol. 129 Ref. 1592).

Benwell MEM, Balfour DJK, Anderson JM. Evidence that tobacco smoking increases the density of (–)-[^{3}H]nicotine binding sites in human brain, *Journal of Neurochemistry* 1988;50:1243-1247. *See* AR (Vol. 136 Ref. 1570).

[55] The tobacco industry cites the opinions of several physicians and scientists to support the contention that nicotine is not addictive. In most cases, as described below, the opinions have been taken out of context, and the cited individuals are on record as believing that nicotine is addictive. Those individuals who agree with the industry that nicotine is not addictive comprise a "handful of scientific supporters." Hwang SL, Ono Y. Tobacco dream team: experts who insist nicotine isn't addictive. *Wall Street Journal* (Mar. 23, 1995). *See* AR (Vol. 711 Ref. 29).

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intoxication, withdrawal, and tolerance." Although withdrawal and tolerance are still considered criteria for addiction, "intoxication" has not been considered a necessary criterion for over thirty years. The industry cites no medical dictionary, expert panel, or scientific organization for this specific definition; the "criteria" are instead extracted from portions of a definition developed in the 1950's and used by the editors of the 1964 Surgeon General's Report on tobacco.[56] This definition was premised on the now-discarded, early twentieth-century conception of drug addiction as a personality disorder characterized by weakness of will, immaturity of character development, and immorality.[57]

Within months of publication of the Surgeon General's Report in 1964, its definition of addiction was cast aside by the scientific community. In a major report, the World Health Organization (WHO) recognized that intoxication was not a distinguishing characteristic of dependence for any drug under its purview.[58] Indeed, people dependent on stable daily doses of opiates may display no observable signs of intoxication.[59] Conversely, it is widely known that nonaddicting drugs such as antihistamines and atropine and scopolamine preparations can produce intoxication.[60] Moreover, under the

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[56] Department of Health, Education, and Welfare, Public Health Service, *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service* (Washington DC: GPO, 1964), at 349-352. *See* AR (Vol. 43 Ref. 156).

[57] Surgeon General's Report, 1988, at 248. *See* AR (Vol. 129 Ref. 1592).

[58] WHO Expert Committee on Addiction-Producing Drugs, *WHO 1964*, World Health Organization Technical Report Series No. 273, Thirteenth Report (Geneva: World Health Organization, 1964), at 3-20. *See* AR (Vol. 43 Ref. 169).

[59] Surgeon General's Report, 1988, at 251. *See* AR (Vol. 129 Ref. 1592).

[60] Garrison JC, Histamine, bradykinin, 5-hydroxytryptamine, and their antagonists, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 23, at 584, 586. *See* AR (Vol. 711 Ref. 14).

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old definition, cocaine and amphetamines would not clearly have been considered addictive because of lack of evidence at the time demonstrating physical dependence.[61] The scientific community thus rejected the old definition of addiction because of new scientific insights about the nature of addiction, more than 15 years before finding nicotine to be addictive.

Today, drug addiction has been defined by scientific organizations from both laboratory and clinical perspectives. The laboratory perspective assesses experimentally whether a substance alters the central nervous system in a manner that can produce characteristic addictive behavior in humans.

While the laboratory perspective focuses on the chemical substance, the clinical perspective on drug addiction assesses whether an individual in society consumes the substance in a manner that demonstrates addiction. Consensus clinical criteria for diagnosing addiction have been developed by the American Psychiatric Association and were most recently published in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) in 1994:

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Criteria for Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) tolerance, as defined by either of the following:

Brown JH. Atropine, scopalomine, and related antimuscarinic drugs, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 8th ed. (New York: Pergamon Press, 1990), chap. 8, at 157. *See* AR (Vol. 711 Ref. 14).

[61] WHO Expert Committee on Addiction-Producing Drugs, *WHO 1964*. World Health Organization Technical Report Series No. 273, Thirteenth Report (Geneva: World Health Organization, 1964), at 3-20. *See* AR (Vol. 43 Ref. 169).

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(a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect

(b) markedly diminished effect with continued use of the same amount of the substance

(2) withdrawal, as manifested by either of the following

(a) the characteristic withdrawal syndrome for the substance . . .

(b) *the same (or a closely related) substance is* taken to relieve or avoid withdrawal symptoms

(3) the substance is often taken in larger amounts or over a longer period than was intended

(4) there is a persistent desire or unsuccessful efforts to cut down or control substance use

(5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects

(6) important social, occupational, or recreational activities are given up or reduced because of substance use

(7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)[62]

Clinicians rely on these criteria to identify addictive behavior in patients.

In 1988, the U.S. Surgeon General used the most up-to-date laboratory tests and clinical criteria to develop the following consensus set of criteria for drug dependence:

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Criteria for Drug Dependence.

Primary Criteria

- Highly controlled or compulsive use
- Psychoactive effects
- Drug-reinforced behavior

Additional Criteria

- Addictive behavior often involves:

[62] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 181. *See* AR (Vol. 37 Ref. 8).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

-stereotypic patterns of use
-use despite harmful effects
-relapse following abstinence
-recurrent drug cravings

- Dependence-producing drugs often produce:
-tolerance
-physical dependence
-pleasant (euphoriant) effects[63]

The laboratory and clinical perspectives on drug addiction embodied in the criteria of the U.S. Surgeon General and the American Psychiatric Association are entirely consistent. Moreover, the definitions of addiction used by all other world scientific authorities, such as WHO[64] and the Royal Society of Canada,[65] share the same principles, differing from each other only in wording and emphasis.

To assess whether nicotine is addictive and whether consumers are addicted to nicotine, FDA utilized these modern laboratory and clinical perspectives on addiction supported in principle by every relevant medical authority in the world.

The modern conception of addiction is not hazy. It does not—as the tobacco industry asserts in its comments—encompass food ingredients, activities, or daily rituals. The scientifically accepted method of identifying addictive drugs emphasizes the *pharmacological* basis of addiction, rather than the simple observation of compulsive-appearing behavior. Addictive drugs are now known to exert "psychoactive" or mood-

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[63] Surgeon General's Report, 1988, at 7. *See* AR (Vol. 129 Ref. 1592).

[64] WHO. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines* (Geneva: World Health Organization, 1992), at 75-76. *See* AR (Vol. 43 Ref. 175).

[65] Royal Society of Canada, *Tobacco, Nicotine, and Addiction: A Committee Report*, prepared at the request of the Royal Society of Canada for the Health Protection Branch, Health and Welfare Canada (Aug. 31, 1989), at v. *See* AR (Vol. 62 Ref. 814).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

altering effects and to affect the structure and function of certain key portions of the brain that motivate repeated, compulsive use of the substance. By activating, inhibiting, or mimicking normal central nervous system processes, dependence-producing drugs exert control over the behavior of users. Consumers are strongly compelled to consume these substances for the pharmacological effect of satisfying addiction. Methods used to identify addictive drugs effectively exclude jogging, eating chocolate, playing computer games, or similar activities because these activities do not depend upon an exogenously administered drug.

Contrary to the suggestion of the tobacco industry, application of the criteria for identifying addictive drugs by the expert organizations responsible for this task[66] shows remarkable consistency across organizations and has resulted in the current identification of a very small number of truly dependence-producing drugs and drug types. These are cocaine, amphetamines, nicotine/tobacco, alcohol, hallucinogens, inhalants, cannabis, phencyclidine, opioids (including morphine and heroin), and the class of sedatives, hypnotics, and anxiolytics.[67] Application of the criteria has not led to the classification of

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[66] These organizations include the World Health Organization's Expert Committee on Drug Dependence, the U.S. Drug Enforcement Administration, the National Institute on Drug Abuse, and the Food and Drug Administration.

[67] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 175-177. *See* AR (Vol. 37 Ref. 8).

WHO, *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines* (Geneva: World Health Organization, 1992), at 75-76. *See* AR (Vol. 43 Ref. 175).

Since no two of these substances are chemically or biologically identical, no two addictions are exactly the same. The observation that dependence on nicotine can be distinguished in some respects from other addictions (as repeatedly asserted by tobacco industry comments) is thus irrelevant to whether nicotine should be classified as addictive.

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carrots or jogging or any of the other activities claimed by the tobacco industry in its comments as "addictive drugs." A key reason for the reliability and validity of the modern definition of drug addiction is that scientific organizations rely upon the convergence of results from several different test procedures before determining that a substance is addictive. In assessing whether nicotine is addictive, FDA examined a wide range of such laboratory evidence, as well as epidemiological evidence of whether consumers are addicted to tobacco products.

c. Data Establish That Nicotine Is Addictive and That Consumers Use Cigarettes and Smokeless Tobacco To Satisfy an Addiction

Animal and human studies demonstrate that nicotine is a powerful psychoactive agent that can cause dependence by producing effects in the brain characteristic of other addictive substances. These findings have been widely published and presented and discussed at major international scientific and medical meetings since the 1980's. Numerous laboratories throughout the world have replicated the core findings using a variety of techniques and have produced convergent results, demonstrating that the findings are reliable and valid. A wealth of epidemiological studies complements these laboratory data by showing that smokers and users of smokeless tobacco display clinical signs and symptoms of addiction. The evidence that has led to the nearly universal scientific conclusion that nicotine is addictive is discussed in the following sections.

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i. Laboratory Studies Establish That Nicotine Produces Pharmacological Effects Similar to Those of Other Addictive Substances. The tests used by the U.S. Surgeon General to develop its consensus definition of drug dependence are the following:

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- Animal and human "drug discrimination" tests, which assess a substance's ability to produce psychoactive effects that can be distinguished from those of other psychoactive substances;
- Tests of human psychoactive or "subjective" effects, which assess a substance's ability to produce changes in perception, mood, and behavior;
- Human and animal drug "self-administration" tests, which assess a substance's ability to induce repeated, compulsive use by functioning as a "positive reinforcer"; and
- Tests for physiological dependence, which assess a substance's ability to produce tolerance and a withdrawal syndrome.

These tests of an addictive drug are widely accepted for their validity.[68] They are the screening tests for addictiveness used most commonly by pharmaceutical manufacturers and regulatory agencies, as evidenced by their prominence in reports by WHO, reviews by the National Institute on Drug Abuse (NIDA) and the College on Problems of Drug Dependence, and deliberations by the Drug Abuse Advisory Committee, which primarily serves FDA.[69]

Thus, these tests were not invented or selectively used to evaluate nicotine. Rather, they have been used to screen drugs of abuse for more than two decades before FDA's current deliberations concerning nicotine. Upon review of the evidence in the

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[68] Surgeon General's Report, 1988, at 270-296. *See* AR (Vol. 129 Ref. 1592).

Balster RL, Drug abuse potential evaluation in animals, *British Journal of Addiction* 1991;86:1549-1558. *See* AR (Vol. 8 Ref. 89).

[69] Surgeon General's Report, 1988, at 269-270. *See* AR (Vol. 129 Ref. 1592).

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administrative record, FDA concludes that nicotine tests positive in all relevant laboratory tests for addictive potential.

Testing for psychoactivity. Psychoactivity is a hallmark characteristic of all dependence-producing drugs. Psychoactive effects (sometimes also referred to as "subjective effects") are changes in mood or feelings that result from the pharmacological effects of the substance on the central nervous system. Changes in mood or feelings that are not produced pharmacologically are not considered psychoactive effects. The psychoactivity of a drug is evaluated in "drug discrimination" studies and "subjective effects" studies.

Drug discrimination studies. Drug discrimination studies evaluate the psychoactivity of a drug by testing whether animal or human subjects can reliably differentiate the drug from placebo. A drug that can be so differentiated is considered a "discriminative stimulus." The tests allow direct comparisons of a drug's effects to known dependence-producing drugs.[70] The drug discrimination paradigm is routinely used in preclinical assessment of the abuse potential of a drug and is considered to be an animal model for human subjective reactions to drugs.[71]

Like other dependence-producing drugs, including cocaine, amphetamine, morphine, marijuana, and alcohol, nicotine tests positive in animal drug discrimination tests. FDA referred to numerous studies documenting this result in the Jurisdictional Analysis and its appendix.[72] Using a variety of drug discrimination paradigms, researchers have shown that

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[70] Balster RL. Drug abuse potential evaluation in animals, *British Journal of Addiction* 1991;86:1549-1558. *See* AR (Vol. 8 Ref. 89).

[71] Surgeon General's Report, 1988, at 274-275. *See* AR (Vol. 129 Ref. 1592).

[72] *See* appendix 1 to Jurisdictional Analysis at 23-25. *See* AR (Vol. 1 Appendix 1).

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nicotine can serve as a discriminative stimulus in rats[73] and squirrel monkeys.[74] Comparative studies have demonstrated that, although nicotine's stimulus effects are unique, they more closely resemble the stimulus effects elicited by amphetamine[75] than those of opioids, sedatives, or hallucinogens.[76]

Nicotine's positive results in these drug discrimination tests are a consequence of its action in the central nervous system. Mecamylamine, a nicotine antagonist that acts in the brain, attenuates nicotine's ability to serve as a discriminative stimulus, whereas the peripheral antagonist hexamethonium—which does not enter the brain—does not affect nicotine

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[73] Morrison CF, Stephenson JA, Nicotine injections as the conditioned stimulus in discrimination learning, *Psychopharmacologia* 1969;15:351-360. *See* AR (Vol. 41 Ref. 107).

Chance WT, Murfin D, Krynock GM, *et al.*, A description of the nicotine stimulus and tests of its generalization to amphetamine, *Psychopharmacology* 1977;55:19-26. *See* AR (Vol. 37 Ref. 22).

Stolerman IP, Discriminative stimulus effects of nicotine in rats trained under different schedules of reinforcement, *Psychopharmacology* 1989;97:131-138. *See* AR (Vol. 42 Ref. 152).

Craft RM, Howard JL, Cue properties of oral and transdermal nicotine in the rat, *Psychopharmacology* 1988;96:281-284. *See* AR (Vol. 74 Ref. 115).

Stolerman IP, Garcha HS, Pratt JA, *et al.*, Role of training dose in discrimination of nicotine and related compounds by rats, *Psychopharmacology* 1984;84:413-419. *See* AR (Vol. 8 Ref. 90-5).

Garcha HS, Goldberg SR, Reavill C, *et al.*, Behavioral effects of the optical isomers of nicotine and nornicotine, and cotinine, in rats, *British Journal of Pharmacology* 1986;88:298. *See* AR (Vol. 38 Ref. 44).

[74] Takada K, Swedberg MDB, Goldberg SR, *et al.*, Discriminative stimulus effects of intravenous l-nicotine and nicotine analogs or metabolites in squirrel monkeys, *Psychopharmacology* 1989;99:208-212. *See* AR (Vol. 43 Ref. 153).

[75] Chance WT, Murfin D, Krynock GM, *et al.*, A description of the nicotine stimulus and tests of its generalization to amphetamine, *Psychopharmacology* 1977;55:19-26. *See* AR (Vol. 37 Ref. 22).

[76] Rosecrans JA, Meltzer LT, Central sites and mechanism of action of nicotine, *Neuroscience and Biobehavioral Reviews* 1981;5(4):497-501. *See* AR (Vol. 42 Ref. 127).

Pratt JA, Stolerman IP, Garcha HS, *et al.*, Discriminative stimulus properties of nicotine: further evidence for mediation at a cholinergic receptor, *Psychopharmacology* 1983;81:54-60. *See* AR (Vol. 8 Ref. 90-2).

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discrimination.[77] These studies demonstrate that nicotine's psychoactive effects are the direct results of its actions in the brain.

Human drug discrimination tests for nicotine are also positive. Using a drug discrimination procedure analogous to those employed with animals, Kallman and colleagues originally demonstrated that nicotine, as delivered by the inhalation of tobacco smoke, acts as a discriminative stimulus in humans.[78] Recently, Perkins *et al.* demonstrated that intranasally administered nicotine also functions as a discriminative stimulus in human volunteers. This result from a product that produces no sensory effects from smoke confirms that the pharmacological action of nicotine—rather than the taste or flavor of tobacco smoke—produces these hallmark psychoactive effects.[79]

Psychoactive effects. Psychoactive or subjective effects produced by addictive drugs may range from very mild relaxation to intense intoxication or impaired cognitive abilities.[80] Assessment in humans of the subjective effects of addictive drugs involves giving either drug or placebo to volunteers and then asking them to report what they feel.

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[77] Rosecrans JA, Chance WT, Cholinergic and non-cholinergic aspects of the discriminative stimulus properties of nicotine, in *Discriminative Stimulus Properties of Drugs*, ed. Lal H (New York: Plenum Press, 1977), at 155-185. *See* AR (Vol. 42 Ref. 126).

Rosecrans JA, Meltzer LT, Central sites and mechanism of action of nicotine, *Neuroscience and Biobehavioral Reviews* 1981;5(4):497-501. *See* AR (Vol. 42 Ref. 127).

Meltzer LT, Rosecrans JA, Aceto MD, *et al.*, Discriminative stimulus properties of the optical isomers of nicotine, *Psychopharmacology* 1980;68:283-286. *See* AR (Vol. 41 Ref. 106).

[78] Kallman WM, Kallman MJ, Harry GJ, *et al.*, Nicotine as a discriminative stimulus in human subjects, in *Drug Discrimination: Applications in CNS Pharmacology*, eds. Colpaert FC, Slangen JL (Amsterdam: Elsevier Biomedical Press, 1982), at 211-218. *See* AR (Vol. 41 Ref. 89).

[79] Perkins K, Grobe J, Scierka A, *et al.*, Discriminative stimulus effects of nicotine in smokers, in *International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II*, eds. Clarke PBS, Quik M, Thurau K, Adlkofer F (Basel: Birkhauser Verlag, 1994), at 111. *See* AR (Vol. 42 Ref. 111).

[80] Surgeon General's Report, 1988, at 270. *See* AR (Vol. 129 Ref. 1592).

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Individuals with histories of addictive drug use report what drug, if any, the test drug feels like. This testing helps determine whether the test drug produces any effects on mood and feeling that resemble those of previously studied drugs. Individuals with histories of using a variety of addictive drugs and who report "liking" the effects of several types of drugs help assess the addictiveness of the test drug. These individuals are asked to evaluate the ability to feel a drug effect, to rate how much they "like" the drug effect, and to attempt to identify the drug that was given from a list of widely used and abused drugs. Results that show consistent kinds of effects across drugs confirm that these drugs are appropriately categorized together as addicting drugs.[81]

Nicotine produces significant psychological sensations whether inhaled or injected. In one study, smokers with histories of abuse of other drugs identified intravenous or inhaled nicotine as being a euphoriant similar to cocaine or amphetamine.[82] With a common measure of the subjective effects of addictive drugs (the Addiction Research Center Inventory), nicotine produced dose-related increases in the "euphoria" scale (also known as the Morphine-Benzedrine Group Scale or MBG) and the "liking" scale, showing that nicotine produces subjective effects similar to those of other addictive drugs. This study essentially extended the original finding of Johnston in 1942, who had argued from the premise that "smoking tobacco is essentially a means of administering nicotine, just as smoking opium is a means of administering morphine."[83] In his study, Johnston administered intravenous injections

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[81] *Id.* at 271-272.

[82] Henningfield JE, Miyasato K, Jasinski DR. Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. *Journal of Pharmacology and Experimental Therapeutics* 1985;234:1-12. *See* AR (Vol. 39 Ref. 69).

[83] Johnston LM. Tobacco smoking and nicotine. *Lancet* 1942;2:742. *See* AR (Vol. 278 Ref. 3947).

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of nicotine, in doses comparable to those that people obtain from cigarettes or smokeless tobacco, to cigarette smokers to determine both nicotine's effects and its potential usefulness in helping people abstain from tobacco. He found that the nicotine injections produced "psychic" effects that "closely resembled" those of cigarette smoke inhalation, were pleasant for smokers, and left the smokers "disinclined to smoke." *See also* section II.C.6.b. (comment 1).

Similar findings were also obtained in a study by Jones *et al.*, who found that intravenous nicotine injections in doses comparable to those that people obtain from cigarettes or smokeless tobacco produced "a pleasurable stimulant-like sensation that many of them termed a 'rush.'" Half of the subjects tested requested substantially higher doses.[84] More recently, these early results have been confirmed by Pomerleau and Pomerleau, Perkins *et al.*, and Sutherland *et al.*, who have found that nicotine delivered from cigarettes, intravenous injection, and intranasal spray produces psychoactive and mood-altering effects consistent with those of other addictive drugs.[85]

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[84] Jones RT, Farrell TR III, Herning RI, Tobacco smoking and nicotine tolerance, in *Self-Administration of Abused Substances: Methods for Study*, ed. Krasnego NA, NIDA Research Monograph 20 (Rockville MD: National Institute on Drug Abuse, 1978), at 202-208. *See* AR (Vol. 41 Ref. 88).

[85] Pomerleau CS, Pomerleau OF, Euphoriant effects of nicotine in smokers, *Psychopharmacology* 1992;108:460-465. *See* AR (Vol. 87 Ref. 426).

Perkins KA, Grobe JE, Epstein LH, *et al.*, Effects of nicotine on subjective arousal may be dependent on baseline subjective state, *Journal of Substance Abuse* 1992;4:131-141. *See* AR (Vol. 348 Ref. 5516).

Perkins KA, Grobe JE, Epstein LH, *et al.*, Chronic and acute tolerance to subjective effects of nicotine, *Pharmacology, Biochemistry and Behavior* 1993;45:375-381. *See* AR (Vol. 271 Ref. 3728).

Sutherland G, Stapleton JA, Russell MAH, *et al.*, Randomised controlled trial of nasal nicotine spray in smoking cessation, *Lancet* 1992;340:324-329. *See* AR (Vol. 91 Ref. 527).

Sutherland G, Russell MA, Stapleton J, *et al.*, Nasal nicotine spray: a rapid nicotine delivery system, *Psychopharmacology* 1992;108:512-518. *See* AR (Vol. 91 Ref. 526).

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The tobacco industry contends that tobacco is used for pleasure. So, too, is cocaine used for pleasure. These data establish, however, that receiving nicotine through a route that does not provide any sensory qualities of tobacco use (e.g., through the venous system) also is pleasurable. Thus, the pharmacological effects of nicotine administered through non-inhalation routes are able to produce the characteristic psychoactive effects of tobacco use.

Self-administration testing. In self-administration testing, human or animal subjects are given access to a drug and then evaluated for their tendency to seek repeated doses of the drug. The self-administration test determines the ability of a drug to sustain drug-seeking behavior—one of the key distinguishing features of drug dependence. The self-administration test is widely used to determine whether a drug can control behavior; a drug whose intake leads to more consumption is called a "positive reinforcer." It is generally accepted in the scientific community that the ability of addictive drugs to serve as positive reinforcers is the core property that promotes the development and maintenance of addiction.[86]

Self-administration procedures using primates and rats have been shown to be valid and reliable predictors of the potential for a compound to result in drug dependence. There is a strong correlation between the types of drugs that serve as reinforcers in animals and the drugs associated with addiction in humans.[87]

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Henningfield JE, Miyasato K, Jasinski DR. Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. *Journal of Pharmacology and Experimental Therapeutics*, 1985;234(1):1-12. *See* AR (Vol. 39 Ref. 69).

[86] Balster RL. Drug abuse potential evaluation in animals. *British Journal of Addiction* 1991;86:1549-1558. *See* AR (Vol. 8 Ref. 89).

[87] Griffiths RR, Bigelow GE, Henningfield JE. Similarities in animal and human drug-taking behavior. *Advances in Substance Abuse* 1980;1:1-90. *See* AR (Vol. 8 Ref. 91-2).

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Animal self-administration studies, using a variety of administration schedules and controls, have shown that nicotine functions as a positive reinforcer across several species.[88] Nicotine is more avidly self-administered when available on an intermittent schedule than when freely available.[89] Since tobacco users self-administer intermittent doses of nicotine per cigarette or pinch of smokeless tobacco, the schedule of nicotine administration that is most reinforcing in animals corresponds to the pattern of actual tobacco consumption.

Consistent with animal self-administration studies, analogous studies with humans in the 1980's demonstrated that nicotine serves as a positive reinforcer under controlled laboratory conditions.[90] Subjects self-administered intravenous nicotine in a regular and

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Woolverton WL, Nader MA. Experimental evaluation of the reinforcing effects of drugs. in *Modern Methods in Pharmacology*, eds. Adler MW, Cowen A (New York: Wiley-Liss, 1990), 6:165-192. *See* AR (Vol. 535 Ref. 96, vol. III.N).

[88] Goldberg SR, Spealman RD, Goldberg DM. Persistent behavior at high rates maintained by intravenous self-administration of nicotine. *Science* 1981;214:573-575. *See* AR (Vol. 5 Ref. 35-2).

Goldberg SR, Spealman RD. Maintenance and suppression of behavior by intravenous nicotine injections in squirrel monkeys. *Federation Proceedings* 1982;41(2):216-220. *See* AR (Vol. 39 Ref. 52).

Spealman RD, Goldberg SR. Maintenance of scheduled-controlled behavior by intravenous injections of nicotine in squirrel monkeys. *Journal of Pharmacology and Experimental Therapeutics* 1982;223(2):402-408. *See* AR (Vol. 42 Ref. 146).

Risner ME, Goldberg SR. A comparison of nicotine and cocaine self-administration in the dog: fixed-ratio and progressive-ratio schedules of intravenous drug infusion. *Journal of Pharmacology and Experimental Therapeutics* 1983;224(2):319-326. *See* AR (Vol. 42 Ref. 119).

Cox BM, Goldstein A, Nelson WT. Nicotine self-administration in rats. *British Journal of Pharmacology* 1984;83:49-55. *See* AR (Vol. 8 Ref. 93-1).

Slifer BL, Balster RL. Intravenous self-administration of nicotine: with and without schedule-induction. *Pharmacology, Biochemistry and Behavior* 1985;22:61-69. *See* AR (Vol. 8 Ref. 93-3).

Corrigall WA, Coen KM. Nicotine maintains robust self-administration in rats on a limited access schedule. *Psychopharmacology* 1989;99:473-478. *See* AR (Vol. 347 Ref. 5495).

[89] Surgeon General's Report, 1988, at 182-189. *See* AR (Vol. 129 Ref. 1592).

[90] Henningfield JE, Miyasoto K, Jasinski DR. Cigarette smokers self-administer intravenous nicotine. *Pharmacology, Biochemistry and Behavior* 1983;19:887-890. *See* AR (Vol. 8 Ref. 97).

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orderly pattern, giving themselves amounts of nicotine comparable to those they were accustomed to receiving from their cigarettes. These studies demonstrate that the pharmacological effects of nicotine can explain why people engage in compulsive consumption of tobacco.

At a molecular level, nicotine's reinforcing effects are widely believed to be a consequence of its actions on specific areas in the central nervous system. Within the scientific community, a consensus has emerged that nicotine, like other addictive drugs such as cocaine, amphetamine, and morphine, causes addiction by increasing the activity of the neurotransmitter dopamine within the mesolimbic system of the brain.[91] A very recent study, which expands on and confirms earlier studies, has demonstrated that nicotine, at doses known to be self-administered, mimics the effects of cocaine, morphine, and amphetamines in the mesolimbic system, by selectively increasing dopamine transmission and energy metabolism in a specific region of the nucleus accumbens previously shown to be important in mediating the addictive effects of these drugs.[92]

Surgeon General's Report, 1988, at 192. *See* AR (Vol. 129 Ref. 1592).

[91] Clarke PBS. Mesolimbic dopamine activation—the key to nicotine reinforcement? *CIBA Foundation Symposium* 1990;152:153-168. *See* AR (Vol. 3 Ref. 19-2).

Corrigall WA, Coen KM. Selective dopamine antagonists reduce nicotine self-administration. *Psychopharmacology* 1991;104:171-176. *See* AR (Vol. 66 Ref. 30).

Corrigall WA, Franklin KBJ, Coen KM, *et al.*, The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. *Psychopharmacology* 1992;107:285-289. *See* AR (Vol. 8 Ref. 93-4).

Iverson LL, . . . harmful to the brain. *Nature* 1996;382:206-207. *See* AR (Vol. 711 Ref. 51).

[92] Pontieri FE, Tanda G, Orzi F, *et al.*, Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature* 1996;382:255-257. *See* AR (Vol. 711 Ref. 51).

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Observing that food, water, and salt also increase dopamine activity in the mesolimbic system, the tobacco industry comments that nicotine's action is not unique. FDA's finding, however, is not that nicotine's role in this system is unique, but that it is *significant*. Indeed, the tobacco industry's own observation on food, water, and salt reflects the significance of nicotine's action. As researchers have noted, the mesolimbic "reward" system of the brain naturally reinforces the intake of essential substances (such as food, water, and salt) because these substances are necessary for human existence. Without an intrinsic reward for eating and drinking, humans would perish. Researchers believe that addictive substances such as nicotine, amphetamine, cocaine, and morphine are so powerful precisely because they activate and even control this natural system of reward. Indeed, the same scientists quoted by the tobacco industry state that "nicotine could substitute for food or other reinforcers" in the mesolimbic system.[93] That nicotine can mimic life-sustaining substances and alter such a pivotal neurological system demonstrates its substantial effect on the structure and function of the human body.

Withdrawal and tolerance. Documentation of a drug withdrawal syndrome is the primary method of establishing that a substance causes physical dependence. According to the Surgeon General, "[m]easurement of drug withdrawal phenomena entails recording physiological, subjective, and behavioral responses that occur when drug administration is terminated."[94] Numerous studies document a characteristic withdrawal syndrome.

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[93] Mifsud JC, Hernandez L, Hoebel BG. Nicotine infused into the nucleus accumbens increases synaptic dopamine as measured by in vivo microdialysis. *Brain Research* 1989;478(2):365-367, at 367. *See* AR (Vol. 535 Ref. 96, vol. III.J).

[94] Surgeon General's Report, 1988, at 291. *See* AR (Vol. 129 Ref. 1592).

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including both physiological and psychological symptoms, associated with nicotine abstinence.[95] Widely used criteria for diagnosing withdrawal come from the American Psychiatric Association's DSM-IV, which defines Nicotine Withdrawal Syndrome as four (or more) of the following symptoms within 24 hours after cessation of use: dysphoric or depressed mood; insomnia; irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain.[96] Although nicotine withdrawal is not as life-threatening as withdrawal from alcohol or some barbiturates, it is comparable to or stronger than withdrawal from such other stimulants as cocaine and can be highly disruptive to personal life.[97] After several weeks of nicotine exposure, users who are deprived of nicotine for more than a few hours can develop withdrawal symptoms.[98] Withdrawal symptoms after quitting tobacco use can persist for months.[99]

The tobacco industry contends that nicotine withdrawal is associated only with psychological changes; the evidence, however, demonstrates that tobacco abstinence also causes significant physiological effects on the body. These effects include decreased heart

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[95] *Id.* at 197-207.

[96] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 244-245. *See* AR (Vol. 37 Ref. 8).

[97] Benowitz NL. Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[98] Jaffe JH. Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-573), at 548. *See* AR (Vol. 535 Ref. 96, vol. III.G).

[99] Ryan FJ. Cold turkey in Greenfield, Iowa: a follow-up study, in *Smoking Behavior: Motives and Incentives*, ed. Dunn WL (Washington DC: VH Winston & Sons, 1973), at 231-234. *See* AR (Vol. 8 Ref. 105).

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rate at rest and after standing, alteration of the electroencephalogram (EEG, a measure of brain electrical activity), skin temperature changes, and disruptions in sleep patterns.[100] Studies have also demonstrated that tobacco withdrawal can cause an increase in weight. This weight increase may be attributed to increased caloric intake, decreased metabolism, and decreased energy expenditure during nicotine withdrawal.[101] The physiological signs of nicotine withdrawal are substantially reversed when nicotine is given in a form other than tobacco.[102]

Significant behavioral and subjective symptoms common to nicotine withdrawal include depression, anger, irritability, anxiety, poor concentration, and restlessness.[103]

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[100] West RJ, Jarvis MJ, Russell MAH, *et al.*, Effect of nicotine replacement on the cigarette withdrawal syndrome, *British Journal of Addiction* 1984;79(2):215-219. *See* AR (Vol. 8 Ref. 102-1).

Hughes JR, Hatsukami D, Signs and symptoms of tobacco withdrawal, *Archives of General Psychiatry* 1986;43:289-294. *See* AR (Vol. 8 Ref. 102-2).

Hughes JR, Higgins ST, Hatsukami D, Effects of abstinence from tobacco: a critical review, *Research Advances in Alcohol and Drug Problems* 1990;10:317-398, at 382. *See* AR (Vol 535 Ref. 96, vol. III.G).

[101] Wack JT, Rodin J, Smoking and its effect on body weight and the systems of caloric regulation, *American Journal of Clinical Nutrition* 1982;35(2):366-380. *See* AR (Vol. 8 Ref. 103-1).

Glauser SC, Glauser EM, Reidenberg MM, *et al.*, Metabolic changes associated with the cessation of cigarette smoking, *Archives of Environmental Health* 1970;20:377-381. *See* AR (Vol. 8 Ref. 103-2).

[102] Surgeon General's Report, 1988, at 208. *See* AR (Vol. 129 Ref. 1592).

[103] *See, e.g.*, Hughes JR, Hatsukami D, Signs and symptoms of tobacco withdrawal, *Archives of General Psychiatry* 1986;43:289-294. *See* AR (Vol. 8 Ref. 102-2).

Centers for Disease Control and Prevention, Reasons for tobacco use and symptoms of nicotine withdrawal among adolescent and young adult tobacco users-United States, 1993, *Morbidity and Mortality Weekly Report* 1994;43(41):745-750. *See* AR (Vol. 7 Ref. 86).

Hughes JR, Nicotine withdrawal, dependence, and abuse, in *DSM-IV Sourcebook*, eds. Widiger T, Frances A, *et al.* (Washington DC: American Psychiatric Association, 1994), 1:109-116. *See* AR (Vol. 535 Ref. 96, vol. III.F).

West RJ, Jarvis MJ, Russell MAH, *et al.*, Effect of nicotine replacement on the cigarette withdrawal syndrome, *British Journal of Addiction* 1984;79(2):215-219. *See* AR (Vol. 8 Ref. 102-1).

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Dependent smokers also show substantial withdrawal symptoms within a day of nicotine abstinence.[104] These psychological symptoms are substantially reversible or preventable by providing nicotine in the form of conventional cigarettes or by providing equivalent or lower doses of nicotine in other forms (e.g., nicotine gum) including forms without the taste of nicotine (e.g., nicotine patches).[105]

Withdrawal from smokeless tobacco also causes physiological changes attributable to nicotine abstinence. Hatsukami and colleagues showed the following changes in users deprived of chewing tobacco: (1) decreased heart rate at rest and after standing; (2) increased craving for tobacco; (3) increased confusion score on the Profile of Mood States (POMS) (this measures tension/anxiety, depression/dejection, confusion, anger/hostility, vigor, and fatigue); (4) increased eating; (5) increased number of sleep interruptions; and (6) increased total scores on a withdrawal symptom checklist for both self-rated and observer-rated measures.[106]

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[104] Jaffe JH. Drug addiction and drug abuse. in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 8th ed. (New York: Pergamon Press. 1990), chap. 22 (522-573), at 548. *See* AR (Vol. 535 Ref. 96, vol. III.G).

[105] Surgeon General's Report, 1988, at 470-485. *See* AR (Vol. 129 Ref. 1592).

Robinson JH, Pritchard WS, Davis RA. Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine. *Psychopharmacology* 1992;108:466-472. *See* AR (Vol. 59 Ref. 236).

Fagerstrom KO, Sawe U, Tonnesen P. Therapeutic use of nicotine patches: efficacy and safety. *Journal of Drug Development* 1993;5:191-205. *See* AR (Vol. 76 Ref. 156).

Fiore MC, Jorenby DE, Baker TB, *et al.*, Tobacco dependence and the nicotine patch. *Journal of the American Medical Association* 1992;268:2687-2694. *See* AR (Vol. 351 Ref. 5609).

[106] Hatsukami DK, Gust SW, Keenan RM. Physiologic and subjective changes from smokeless tobacco withdrawal. *Clinical Pharmacology and Therapeutics* 1987;41:103-107. *See* AR (Vol. 7 Ref. 73).

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A second key test of a substance's ability to produce physical dependence is whether it promotes tolerance.[107] Tolerance occurs when responses produced by an initial dose are diminished with repeated doses, so that increasing doses are necessary to reproduce the initial effects. Tolerance to some effects of a substance can be acute, occurring within hours to days, while tolerance to other effects develops chronically as a result of long-term substance exposure.

Tobacco users become tolerant to nicotine both acutely and chronically.[108] After a single night of abstinence, the nervous system[109] and the cardiovascular system[110] are highly responsive to small doses of nicotine. But after the administration of the equivalent of a few cigarettes, the responsiveness of the human body to nicotine declines markedly. Thus, a cigarette smoked in the middle of the day may not elicit the same psychological or physiological response in a cigarette smoker as one smoked earlier in the morning. This severe degree of acute tolerance seems to greatly exceed that produced by cocaine and to be more comparable to that produced by morphine.[111]

Tolerance to other effects of nicotine develops over weeks and months. For example, new smokers often experience nicotine-related effects such as dizziness, nausea, intoxication, vomiting, and headaches—symptoms that disappear eventually as the

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[107] Surgeon General's Report, 1988, at 50-54. *See* AR (Vol. 129 Ref. 1592).

[108] Perkins KA, Grobe JE, Epstein LH, *et al.*, Chronic and acute tolerance to subjective effects of nicotine, *Pharmacology, Biochemistry and Behavior* 1993;45:375-381. *See* AR (Vol. 271 Ref. 3728).

[109] *Id.*

[110] Surgeon General's Report, 1988, at 47-48. *See* AR (Vol. 129 Ref. 1592).

[111] Jaffe JH, Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-573), at 533, 543, 548. *See* AR (Vol. 535 Ref. 96, vol. III.G).

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smokers' bodies adapt to nicotine and tolerance to these effects develops.[112] These and other examples of chronic tolerance (such as faster nicotine metabolism among experienced smokers) are consistent with laboratory evidence of long-term structural changes in the brain and other parts of the body from nicotine use.[113]

There is also epidemiological evidence that the vast majority of smokers and smokeless tobacco users increase their consumption and usage of tobacco products over time. *See* section II.A.3.c.ii., below. This escalation of dose is an additional demonstration of the development of tolerance. Like users of other addictive drugs, tobacco users eventually reach a stable level of consumption.[114]

Laboratory studies on drug discrimination, psychoactive/subjective effects, self-administration, and withdrawal and tolerance thus demonstrate that nicotine has the properties of an addictive drug.

Nicotine compared to saccharin and caffeine. In its comments, the tobacco industry attempts to discount a multitude of laboratory studies of nicotine by selectively pointing to a single test used to screen for addictive substances and arguing that, in that test, nicotine's effect was similar to saccharin's. From this premise, the industry concludes that nicotine is no more addictive than saccharin. This argument misrepresents the published data on saccharin's and nicotine's properties and overlooks fundamental

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[112] Department of Health and Human Services, Office on Smoking and Health. *Preventing Tobacco Use Among Young People: A Report of the Surgeon General* (Washington DC: Government Printing Office, 1994), at 138. *See* AR (Vol. 133 Ref. 1596).

[113] *See* section II.A.3.i. and ii., below, for a more detailed discussion.

[114] Jaffe JH. Drug addiction and drug abuse. in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-532). *See* AR (Vol. 535 Ref. 96, vol. III.G).

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differences between saccharin and nicotine. Contrary to the tobacco industry's argument, saccharin has not been shown to meet the most fundamental test of an addictive drug, namely, psychoactive effects in the brain that account for its appeal to humans and animals. Nicotine *has* been shown to have these effects.

In contrast to nicotine, which can be pleasurable even when injected intravenously, saccharin is liked primarily because of its taste. For example, rats can be trained to self-administer oral doses of saccharin in preference to water, demonstrating only that rats prefer the taste of saccharin to that of water. FDA is unaware of any studies, and the tobacco industry cites none, in which rats have self-administered saccharin intravenously. Such a study would be an essential step in proving that saccharin's appeal lies in its effects on the brain. Moreover, there is no evidence that saccharin produces any psychoactive effects. In contrast, nicotine, which produces no such pleasant taste, demonstrates all of the properties of an addictive drug, including self-administration and psychoactivity, through its actions on the central nervous system.

The tobacco industry also argues that nicotine is similar to caffeine in tests of addictive potential. FDA disagrees. In comparison to the more orderly pattern of self-administration observed with nicotine and stimulant drugs, the pattern of caffeine self-administration is generally weak and sporadic in animals.[115] Hence, in comparison to known

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[115] Heishman SJ, Henningfield JE, Stimulus functions of caffeine in humans: relation to dependence potential, *Neuroscience and Biobehavioral Reviews* 1992;16:273-287. *See* AR (Vol. 79 Ref. 230).

Griffiths RR, Woodson PP, Reinforcing properties of caffeine: studies in humans and laboratory animals, *Pharmacology, Biochemistry and Behavior* 1988;29(2):419-427. *See* AR (Vol. 535 Ref. 96, vol. III.E).

Jaffe JH. Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522–573), at 524. *See* AR (Vol. 535 Ref. 96, vol. III.G).

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drugs of dependence (e.g., cocaine, morphine, and nicotine), caffeine has a lower relative dependence potential as well as a low risk of adverse effects in amounts currently permitted in foods and beverages.[116] Unlike nicotine, caffeine is not recognized as a dependence-producing substance by the American Psychiatric Association[117] and the World Health Organization.[118]

The laboratory differences between nicotine and caffeine are reflected in the different patterns of substance consumption. Neal Benowitz, a prominent addiction researcher, noted that, "[i]n contrast to coffee drinkers, the vast majority of cigarette smokers exhibit addictive behavior."[119] The wide acceptance of decaffeinated beverages demonstrates a much more general ability to control intake and minimize undesirable effects of caffeine. Moreover, while nicotine/tobacco addiction is estimated to be one of the leading causes of premature death in the United States,[120] caffeine at customary doses poses few risks to the individual or to society.

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[116] Heishman SJ, Henningfield JE, Stimulus functions of caffeine in humans: relation to dependence potential. *Neuroscience and Biobehavioral Reviews* 1992;16:273-287. *See* AR (Vol. 79 Ref. 230).

Benowitz NL, Cigarette smoking and nicotine addiction. *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[117] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 176. *See* AR (Vol. 37 Ref. 8).

[118] WHO, *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines* (Geneva: World Health Organization, 1992), at 75-76. *See* AR (Vol. 43 Ref. 175).

[119] Benowitz NL, Cigarette smoking and nicotine addiction. *Medical Clinics of North America* 1992;76(2):415-437, at 430. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[120] McGinnis JM, Foege WH, Actual causes of death in the United States. *Journal of the American Medical Association* 1993;270(18):2207-2212. *See* AR (Vol. 2 Ref. 15-1).

Hearing on Preventive Health: An Ounce of Prevention Saves a Pound of Cure, Before the Special Committee on Aging, U.S. Senate, 103d Cong., 1st Sess. 2 (May 6, 1993) (statement of Roger Herdman, Maria Hewitt, Mary Laschober, on smoking-related deaths and financial costs: Office of Technology Assessment estimates for 1990). *See* AR (Vol. 170 Ref. 2024).

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Thus, the average tobacco consumer—but not the average coffee drinker—uses tobacco despite severe health risks, a clinical sign of addiction.[121]

In summary, widely publicized laboratory studies show that tobacco use, like heroin and cocaine use, is a behavioral-pharmacological process in which the individual's continued consumption of tobacco is controlled by a psychoactive and reinforcing drug that exerts its control through the central nervous system. Thus, nicotine is similar to other addictive drugs in every relevant aspect. For this reason, every scientific authority that has reviewed the results of the laboratory evidence has concluded that nicotine is addictive.

ii. Epidemiological Data Establish That Many Tobacco Users Are Addicted.

Numerous well-publicized studies and health surveys have documented the characteristics of nicotine dependence among tobacco users. In the United States, clinical criteria to assess addiction come from the DSM-IV published by the American Psychiatric Association.

Several large studies have confirmed that most cigarette smokers qualify for a diagnosis of nicotine dependence. As described in depth in the appendix to the Jurisdictional Analysis, and discussed further in section II.B.2.a., below, as many as 92% of smokers are addicted to cigarettes.[122] Smokers are more likely to become addicted than

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[121] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 181. *See* AR (Vol. 37 Ref. 8).

[122] *See* appendix 1 to Jurisdictional Analysis, at 42-47. *See* AR (Vol. 1 Appendix 1).

In the Jurisdictional Analysis (60 FR 41576), FDA referred to rates of dependence among "frequent smokers" as being in the range of 75% to 90%. In this document, FDA does not use "frequent" but rather describes the definition of smokers used in each study. *See* section II.B.2., below.

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users of other dependence-producing drugs, including cocaine, alcohol, marijuana, inhalants, and heroin.[123] Consistent with the results from these large studies, which assessed the prevalence of nicotine dependence as defined by meeting three or more of the seven criteria for addiction, are the findings of other studies that assessed the proportion of tobacco users meeting individual criteria. Of the seven criteria listed in section II.A.3.b., above, DSM-IV observes that six are readily apparent among tobacco users: desire to quit or unsuccessful efforts to cut down, use continued despite medical problems, a great deal of time spent using, use of substance in larger amounts and longer than intended, withdrawal, and tolerance.[124] These results strongly support the conclusion that addiction to nicotine is widespread among smokers.

Although there have been no population-based studies using criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) to assess rates of addiction to smokeless tobacco, substantial evidence demonstrates that a high proportion of smokeless tobacco users meet individual DSM criteria for addiction. This evidence strongly supports the conclusion that a substantial proportion of such users are addicted. In 1992, the Inspector General of the Department of Health and Human Services estimated that approximately 75% of young regular users of smokeless tobacco are addicted.[125]

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[123] Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from the National Comorbidity Survey, *Experimental and Clinical Psychopharmacology* 1994;2:244-268. *See* AR (Vol. 37 Ref. 4).

[124] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 243. *See* AR (Vol. 37 Ref. 8).

[125] Department of Health and Human Services, Office on Smoking and Health. *Spit Tobacco and Youth* (Washington DC: GPO, 1992), at 8. *See* AR (Vol. 7 Ref. 76).

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Data demonstrating that a high proportion of smokers and users of smokeless tobacco meet individual DSM criteria for addiction are now discussed.

Desire to quit or unsuccessful efforts to cut down. Each year, more than 15 million people in the United States—almost one-third of all daily smokers—try to quit smoking. Fewer than 3% of smokers achieve 1 year of abstinence.[126]

Quitting smokeless tobacco is also difficult. In one study, only 2.3% of smokeless tobacco users at a cessation clinic were able to remain abstinent for 6 months; the study concluded that using smokeless tobacco may be more addicting than cigarette smoking.[127]

The Centers for Disease Control and Prevention (CDC) found that the greater the level of use of the tobacco product, the more likely young people were to report that "it's really hard to quit." This increase in difficulty quitting as the amount of tobacco consumed increases demonstrates a dose-response relationship, one of the characteristic features of pharmacological effects. This dose-response relationship holds true for both cigarettes and smokeless tobacco used by 10- to 22-year-olds. For example, 74% of young people who used smokeless tobacco every day reported that it was very difficult to quit, compared to only 11% who used smokeless tobacco 1 to 14 days a month.[128]

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[126] Centers for Disease Control and Prevention, Smoking cessation during previous year among adults—United States, 1990 and 1991, *Morbidity and Mortality Weekly Report* 1993;42(26):504-507. *See* AR (Vol. 66 Ref. 2).

[127] Glover ED, Glover PN, Smokeless tobacco cessation and nicotine reduction therapy, in *Smokeless Tobacco or Health, an International Perspective*, Smoking and Tobacco Control, *NIDA Research Monograph* 2, NIH Publication No. 93-3461 (Rockville MD: Government Printing Office, 1993), at 291-295. *See* AR (Vol. 7 Ref. 79-1).

[128] Centers for Disease Control and Prevention, Reasons for tobacco use and symptoms of nicotine withdrawal among adolescents and young adult tobacco users—United States, 1993, *Morbidity and Mortality Weekly Report* 1994;43(41):745-750. *See* AR (Vol. 7 Ref. 86).

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Additional studies on the common desire to quit and the failure of the vast majority of attempts can be found in appendix 1 to Jurisdictional Analysis.[129]

Use continued despite medical problems. As many as 90% of smokers know that tobacco products are harmful to their own health, 65% of current smokers believe that smoking "has already affected" their health, and 77% of smokers believe that they could "avoid or decrease serious health problems from smoking" if they quit.[130] Yet they keep smoking.

Consumers of smokeless tobacco also recognize the health risks of their tobacco use, but do not stop. In one study, 96% of young men who regularly used smokeless tobacco agreed that chewing tobacco and snuff can cause cancer.[131] Another study of users age 17 and over revealed that 77.4% believe that smokeless tobacco is a health hazard.[132]

People even continue tobacco use in the face of life-threatening, tobacco-related illnesses. For example, studies have shown that about half of smokers who have had

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[129] *See* appendix 1 to Jurisdictional Analysis, at 52-55. *See* AR (Vol. 1 Appendix 1).

[130] Gallup GH, *Smoking Prevalence, Beliefs, and Activities by Gender and Other Demographic Indicators* (Princeton NJ: Gallup Organization, 1993). *See* AR (Vol. 38 Ref. 43a).

[131] Department of Health and Human Services. Office on Smoking and Health. *Preventing Tobacco Use Among Young People: A Report of the Surgeon General* (Washington DC: Government Printing Office, 1994), at 101. *See* AR (Vol. 133 Ref. 1596).

[132] Novotny TE, Pierce JP, Fiore MC, *et al.*, Smokeless tobacco use in the United States: the adult use of tobacco surveys. *Monographs/National Cancer Institute* (1989;8:23-28. *See* AR (Vol. 41 Ref. 109).

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surgery for lung cancer resume smoking[133] and that almost 40% of smokers who have had their larynxes removed try smoking again.[134]

Additional data on the use of tobacco products despite the health problems they have caused are presented in appendix 1 to the Jurisdictional Analysis.[135]

Great deal of time spent using. Studies have demonstrated that tobacco users consume tobacco regularly and compulsively. For example, 90% of smokers consume five or more cigarettes every day.[136] Over two-thirds of smokers who consume five cigarettes a day smoke their first cigarette within the first half-hour after awakening;[137] according to many experts, this need is a key symptom indicating a very significant level of dependence.[138]

Among users of chewing tobacco and moist snuff over 18, half use the products every day, and the proportion of daily users rises with age.[139] The Inspector General of

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[133] Davison G, Duffy M, Smoking habits of long term survivors of surgery for lung cancer. *Thorax* 1982;37:331-333. *See* AR (Vol. 6 Ref. 58).

[134] West R, Himbury S, Smoking habits after laryngectomy. *British Medical Journal* 1985;291:514-515. *See* AR (Vol. 6 Ref. 59).

[135] *See* appendix 1 to Jurisdictional Analysis, at 56-58. *See* AR (Vol. 1 Appendix 1).

[136] Benowitz NL, Cigarette smoking and nicotine addiction. *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. IILA).

Henningfield JE, Cohen C, Slade JD. Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991:86:565-569. *See* AR (Vol. 277 Ref. 3904).

[137] Giovino GA, Zhu BP, Tomar S, *et al.*, *Epidemiology of Tobacco Use and Symptoms of Nicotine Addiction in the United States: A Compilation of Data from Large National Surveys*, presentation of the Centers for Disease Control and Prevention to the FDA's Drug Abuse Advisory Committee (Aug. 2, 1994), slide 19 (from National Health Interview Survey 1987). *See* AR (Vol. 459 Ref. 7820).

[138] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), 245. *See* AR (Vol. 37 Ref. 8).

[139] Department of Health and Human Services, National Center for Health Statistics, *Vital and Health Statistics: Smoking and Other Tobacco Use: United States, 1987*, Series 10: Data from the National

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the U.S. Department of Health and Human Services reported that "our 1986 and 1992 users typically held their dip or chaw 25 to 30 minutes, with most keeping it in over 30 minutes, and often up to one hour."[140]

Use of substance in larger amounts or longer than intended. Few beginning smokers plan to become daily smokers. Yet 90% of current smokers consume at least five cigarettes a day.[141] Smokers also smoke for longer periods than they intend. Among high school seniors from the Monitoring the Future Project (1976–86), almost half of the daily smokers reported that they would either probably or definitely not be smoking 5 years after graduation.[142] In a follow-up study conducted 5 to 6 years after graduation, more than two-thirds were smoking as frequently or more frequently than they had in high school (26% were smoking at the same level, and 40% were smoking more).[143]

Other evidence that users of cigarettes and smokeless tobacco consume more than they intend comes from surveys demonstrating that many people try to quit but fail. For

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Health Survey, No. 169, Sep. 1989, DHHS Publication No. (PHS) 89-1597 (Washington DC: Government Printing Office, 1989), at 24, 26. *See* AR (Vol. 711 Ref. 9).

[140] Department of Health and Human Services, Office on Smoking and Health, *Spit Tobacco and Youth* (Washington DC: Government Printing Office, 1992), at 7. *See* AR (Vol. 7 Ref. 76).

[141] Benowitz NL, Cigarette smoking and nicotine addiction. *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. III.A).

Henningfield JE, Cohen C, Slade JD. Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991;86:565-569. *See* AR (Vol. 277 Ref. 39(4).

[142] Ehlers MJ, Perry CL, Eriksen MP, *et al.*, The report of the Surgeon General: preventing tobacco use among young people, *American Journal of Public Health* 1994;84(4):543-547, at 544. *See* AR (Vol. 38 Ref. 39).

[143] *Id.*

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example, two of every five adult users of smokeless tobacco have tried to quit.[144] Additional studies are discussed in detail in appendix 1 to the Jurisdictional Analysis.[145]

Withdrawal. In addition to experimental evidence of withdrawal from nicotine described in section II.A.3.c.i., above, persuasive data from epidemiological studies also demonstrate that the vast majority of consumers who abstain from tobacco products experience withdrawal symptoms.[146]

Studies show that the symptoms of irritability, nervousness, restlessness, and increased appetite each affect over half of abstinent smokers; indeed, about half of abstinent smokers qualify for a formal diagnosis of Nicotine Withdrawal Syndrome under the *Diagnostic and Statistical Manual of Mental Disorders*, 3d ed., revised (DSM-III-R).[147] Withdrawal symptoms show a dose-response relationship; heavier smokers are more likely than light smokers to experience the symptoms of difficulty concentrating, hunger, irritability, restlessness, and sadness when they try to quit.[148] A similar dose-response relationship between the likelihood of withdrawal symptoms and the level of

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[144] Novotny TE, Pierce JP, Fiore MC, *et al.*, Smokeless tobacco use in the United States: the adult use of tobacco surveys, *Monographs/National Cancer Institute* 1989;8:25-28. *See* AR (Vol. 41 Ref. 109).

[145] *See* appendix 1 to Jurisdictional Analysis, at 48-55. *See* AR (Vol. 1 Appendix 1).

[146] *See* appendix 1 to Jurisdictional Analysis, at 58-61. *See* AR (Vol. 1 Appendix 1).

[147] Breslau N, Kilbey MM, Andreski MA, Nicotine withdrawal symptoms and psychiatric disorders: findings from an epidemiologic study of young adults, *American Journal of Psychiatry* 1992;149(4):464-469. *See* AR (Vol. 37 Ref. 18).

[148] Giovino GA, Zhu BP, Tomar S, *et al.*, *Epidemiology of Tobacco Use and Symptoms of Nicotine Addiction in the United States: A Compilation of Data from Large National Surveys*, presentation of the Centers for Disease Control and Prevention to the FDA's Drug Abuse Advisory Committee (Aug. 2, 1994), slides 27-32. *See* AR (Vol. 459 Ref. 7820).

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nicotine intake was found among British schoolgirls[149] and other populations studied.[150] Most people who quit smoking relapse within 1 week,[151] when withdrawal symptoms are at or near their peak.[152]

Smokeless tobacco users typically experience withdrawal symptoms similar to those reported by smokers. In a study of young smokeless tobacco users, over 90% of daily users reported at least one symptom of nicotine withdrawal when trying to discontinue use. Restlessness and irritability were reported by half of daily users during abstinence.[153]

Tolerance. In addition to laboratory measures of tolerance to nicotine described in section II.A.3.c.i., above, epidemiological studies show that users of tobacco products require increasing amounts to maintain the same effects. The 1991 and 1992 National Household Survey on Drug Abuse found that 12% of smokers 25 years or older and 20% of smokers 12 to 24 years of age who smoke 16 to 25 cigarettes per day report feeling the need for an increased number of cigarettes over time to obtain the desired effects.[154]

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[149] McNeill AD, West RJ, Jarvis M, *et al.*, Cigarette withdrawal symptoms in adolescent smokers, *Psychopharmacology* 1986;90(4):533-536. *See* AR (Vol. 95 Ref. 683).

[150] Surgeon General's Report, 1988, at 206-207. *See* AR (Vol. 129 Ref. 1592).

[151] Hughes JR, Gulliver SB, Fenwick JW, *et al.*, Smoking cessation among self-quitters, *Health Psychology* 1992;11:331-334. *See* AR (Vol. 348 Ref. 5512).

[152] Hughes JR, Gust SW, Skoog K, *et al.*, Symptoms of tobacco withdrawal: a replication and extension, *Archives of General Psychiatry* 1991:48:52-59. *See* AR (Vol. 129 Ref. 1404).

[153] Centers for Disease Control and Prevention, Reasons for tobacco use and symptoms of nicotine withdrawal among adolescents and young adult tobacco users—United States, 1993, *Morbidity and Mortality Weekly Report* 1994:43(41):745-750. *See* AR (Vol. 7 Ref. 86).

[154] Giovino GA, Zhu BP, Tomar S, *et al.*, *Epidemiology of Tobacco Use and Symptoms of Nicotine Addiction in the United States: A Compilation of Data from Large National Surveys*, presentation of the Centers for Disease Control and Prevention to the FDA's Drug Abuse Advisory Committee (Aug. 2, 1994), slide 24. *See* AR (Vol. 459 Ref. 7820).

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Among those who have tried an addictive substance at least once, people who have tried cigarettes are more likely to report the need for larger doses to get the same effect than people who have tried cocaine, marijuana, and alcohol.[155]

Most consumers of tobacco products escalate their doses over time. Whereas few cigarette smokers initially plan to be regular daily users, approximately 90% of them consume more than five cigarettes every day.[156]

Smokeless tobacco users also increase their dose of nicotine. One study showed a positive relationship among the number of years of smokeless tobacco use, the number of minutes per day of reported use, and urinary nicotine and cotinine levels.[157] (Cotinine is a major metabolite of nicotine and an indicator of nicotine absorption.) Other studies on dose escalation of tobacco products can be found in appendix 1 to the Jurisdictional Analysis.[158]

The epidemiological data demonstrate that a large proportion of tobacco users are dependent on nicotine and that overwhelming numbers of users show signs of addiction. These data complement laboratory evidence proving that nicotine is an addictive substance and have led to the nearly universal scientific recognition of nicotine as a drug whose

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[155] Henningfield JE, Clayton R, Pollin W. Involvement of tobacco in alcoholism and illicit drug use. *British Journal of Addiction* 1990;85:279-292. *See* AR (Vol. 39 Ref. 66).

[156] Benowitz NL. Cigarette smoking and nicotine addiction. *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. III.A).

Henningfield JE, Cohen C, Slade JD. Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991;86:565-569. *See* AR (Vol. 277 Ref. 3904).

[157] World Health Organization. *Smokeless Tobacco Control: Report of a WHO Study Group*. WHO Technical Report Series No. 773 (Geneva: WHO, 1988), 36. *See* AR (Vol. 7 Ref. 83).

[158] *See* appendix 1 to Jurisdictional Analysis, at 48-51. *See* AR (Vol. 1 Appendix 1).

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pharmacological effects compel continued use. These widely disseminated public findings establish that a reasonable person in the position of a tobacco manufacturer would foresee that tobacco products would be consumed to satisfy an addiction to nicotine.[159]

4. It Is Foreseeable That Consumers Will Use Cigarettes and Smokeless Tobacco for Other Pharmacological Purposes

In addition to its foreseeable addictive effects, nicotine produces a range of other well-known and foreseeable significant pharmacological effects of importance to tobacco users. Evidence demonstrating that consumers actually use tobacco products for these effects is discussed in section II.B.2., below.

Central Nervous System Effects: Sedation, Stimulation, Mood, and Cognition.

Nicotine significantly alters the structure and function of the brain. At the molecular level, nicotine acts by stimulating receptors on the surfaces of brain cells intended for natural neurotransmitters such as acetylcholine and by stimulating the release of other key substances such as dopamine.[160] Nicotine also changes the brain's molecular structure. Extensive animal research by both the tobacco industry and other researchers shows that nicotine exposure, ranging from a few days to a few weeks, within the range of doses equivalent to those received from smoking cigarettes, increases the number and changes the functional activity of nicotine receptors in the brain.[161] In one study, doses of nicotine

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[159] FDA notes that at least one major tobacco company appears to agree that information about the "addicting" properties of cigarettes is so widely disseminated that it must be considered foreseeable. In a lawsuit brought against RJR by a smoker, RJR argued that the "alleged habituating or 'addicting'" qualities of cigarette smoking are so well known that smokers must be held to have foreseen them. *See* section II.C.2.b.iv., below.

[160] *See* the discussion of dopamine in the mesolimbic system, section II.A.3.c.i., above.

[161] Marks MJ, Burch JB, Collins AC. Effects of chronic nicotine infusion on tolerance development and nicotine receptors, *Journal of Pharmacology and Experimental Therapeutics* 1983;226:817-825. *See* AR (Vol. 41 Ref. 103).

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considered equivalent to those received by a fetus of a smoking mother increase the number of nicotine receptors in the brains of newborn rats.[162] Consistent with animal data, cigarette smokers show clear evidence of increased numbers of cerebral nicotine receptors as a consequence of their smoking.[163]

The result of these molecular actions is that nicotine clinically affects arousal, attention, mood, and, under certain conditions, cognition. Depending on the dose and the circumstances, nicotine delivered by cigarette smoking can have an arousal-increasing or arousal-reducing effect.[164] This is another respect in which nicotine is similar to such other addictive drugs as opiates, which can have both stimulating and sedating effects.

Nicotine's effects on mood and arousal have been confirmed using electroencephalographic (EEG) analysis, a measurement of electrical activity in the brain.[165] When smokers are placed in a stressful situation, smoking can have a depressant

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Surgeon General's Report, 1988, at 53-54. *See* AR (Vol. 129 Ref. 1592).

Department of Health and Human Services, Office on Smoking and Health, *Preventing Tobacco Use Among Young People: A Report of the Surgeon General* (Washington DC: GPO, 1994), at 32-33. *See* AR (Vol. 133 Ref. 1596).

[162] Slotkin TA, Orband-Miller L, Queen KL, Development of (^{3}H)nicotine binding sites in brain regions of rats exposed to nicotine prenatally via maternal injections or infusions, *Journal of Pharmacology and Experimental Therapeutics* 1987;242:232-237. *See* AR (Vol. 140 Ref. 1656).

[163] Benwell MEM, Balfour DJK, Anderson JM, Evidence that tobacco smoking increases the density of (–)-[^{3}H]nicotine binding sites in human brain, *Journal of Neurochemistry* 1988;50:1243-1247. *See* AR (Vol. 136 Ref. 1570).

[164] Norton R, Brown K, Howard R, Smoking, nicotine dose and the lateralisation of electrocortical activity, *Psychopharmacology* 1992;108:473-479. *See* AR (Vol. 3 Ref. 22).

[165] Pritchard WS, Gilbert DG, Duke DW, Flexible effects of quantified cigarette-smoke delivery on EEG dimensional complexity, *Psychopharmacology* 1993;113:95-102. *See* AR (Vol. 3 Ref. 23-1).

Pritchard WS, Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490. *See* AR (Vol. 105 Ref. 965).

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effect on the EEG profile.[166] When smokers are placed in conditions of low arousal induced by mild sensory isolation, cigarette smoking can have a stimulant effect.[167] In other words, smoking can have a relaxing effect in stressful situations and a stimulating effect in otherwise nonstimulating circumstances.

The tobacco industry correctly observes that many substances affect the EEG. But what is significant is not *that* nicotine affects the EEG, but *how* nicotine does so. Nicotine's impact on the EEG: (1) is reproducible, (2) is clinically significant, (3) corresponds to other physiological and psychological changes of smoking, and (4) is similar to certain EEG changes associated with other addictive drugs such as benzodiazepines.[168] Altered electrical activity of the brain as demonstrated by EEG is convincing evidence of nicotine's significant pharmacological effects on the structure and function of the body.

Smokers perform better on some cognitive tests than do deprived smokers, but nicotine does not improve general learning or make smokers generally perform better than nonsmokers.[169] One leading researcher noted that, after a few hours of abstinence, "[P]eople are reporting they can't concentrate as well, they can't get the tasks done as

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Golding JF. Effects of cigarette smoking on resting EEG, visual evoked potentials and photic driving. *Pharmacology, Biochemistry and Behavior* 1988;29:23-32. *See* AR (Vol. 3 Ref. 23-3).

[166] Pritchard WS. Electroencephalographic effects of cigarette smoking. *Psychopharmacology* 1991;104:485-490. *See* AR (Vol. 105 Ref. 965).

[167] Golding J, Mangan GL. Arousing and de-arousing effects of cigarette smoking under conditions of stress and mild sensory isolation. *Psychophysiology* 1982;19(4):449-456. *See* AR (Vol. 48 Ref. 101).

[168] Pritchard WS. Electroencephalographic effects of cigarette smoking. *Psychopharmacology* 1991;104:485-490, at 485, 488. *See* AR (Vol. 105 Ref. 965).

[169] Surgeon General's Report, 1988, at 441. *See* AR (Vol. 129 Ref. 1592).

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well, and our objective performance batteries confirm that. They're right . . . it's not just a psychological effect. They really aren't functioning as well."[170]

Evidence on nicotine's effects on mood and cognition is strongly supported by the work of tobacco industry researchers, who concur that people use tobacco for the psychoactive effects of nicotine. These researchers contend that nicotine delivered by tobacco produces psychoactive effects comparable to the effects of prescription tranquilizers. For example, a researcher for the R.J. Reynolds Tobacco Company (RJR), W. S. Pritchard, reported that smoking cigarettes could produce "an EEG effect that in the benzodiazepine literature is associated with anxiety relief," leading him to conclude that "an important smoking motive for deep inhaling smokers might be anxiety reduction" and that his results were consistent with the theory that smoking provides beneficial psychological effects ("psychological tools" or "resources").[171]

In a significant extension of this work, Robinson *et al.* concluded that "the beneficial effects of smoking on cognitive performance are a function of nicotine absorbed from cigarette smoke upon inhalation."[172] These RJR researchers performed their study because they thought that, although earlier work with various nicotine preparations was consistent with the hypothesis that people smoked for "psychopharmacological effects."

[170] Henningfield J. Transcript to the FDA Drug Abuse Advisory Committee, Meeting 27, "Issues Concerning Nicotine-Containing Cigarettes and Other Tobacco Products" (Aug. 2, 1994), at 309. *See* AR (Vol. 255 Ref. 3445).

[171] Pritchard WS. Electroencephalographic effects of cigarette smoking. *Psychopharmacology* 1991;104:485-490, at 485, 488. *See* AR (Vol. 105 Ref. 965).

[172] Robinson JH, Pritchard WS, Davis RA. Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine. *Psychopharmacology* 1992;108:466-472. *See* AR (Vol. 59 Ref. 236).

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the role of nicotine in cigarettes was inconclusive. They therefore compared standard nicotine-delivering cigarettes to cigarettes that were similar in all other relevant characteristics (e.g., similar gases, tar, etc.) but that provided only "trace" or "minimal" levels of nicotine. The regular cigarettes provided psychopharmacological effects, while the minimal nicotine cigarettes did not.

One of the leading tobacco industry-funded proponents of the contention that nicotine is not addictive, D. M. Warburton, is also one of the leading proponents of the view that people smoke because of the pharmacological actions of nicotine in the brain, rather than in the mouth.[173] Warburton argues that nicotine is a "therapeutic agent" that is self-administered by smokers to "control their bodily state"[174] and that "the rapid absorption and rapid metabolism make this substance suitable for hour-by-hour self-medication because of the personal control [over dosage needs] that can be exercised. In this respect nicotine is superior to other compounds for medication."[175] Thus, the conclusions of tobacco industry-funded researchers support FDA's finding that a reasonable manufacturer would foresee that nicotine in tobacco products produces significant pharmacological effects important to users.

Other Effects: Weight Regulation. Nicotine also plays a role in weight regulation. The 1988 Surgeon General's Report summarized the available data:

> In summary, there is substantial evidence of an inverse relationship between cigarette smoking and body weight. Of 71 studies reported since 1970, 62 (87%) collectively indicate that smokers

[173] Warburton DM. Nicotine: an addictive substance or a therapeutic agent. *Progress in Drug Research* 1989;33:9-41. *See* AR (Vol. 140 Ref. 1657).

[174] *Id.* at 11.

[175] *Id.* at 37.

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> weigh less than nonsmokers and that people who quit smoking gain weight. . . .
>
> Animal studies indicate that nicotine administration results in weight loss or decreased weight gains and that cessation of nicotine results in body weight gains greater than those of controls [animals that did not receive nicotine]. . . .
>
> Recent research on nicotine polacrilex gum with humans corroborates the role of nicotine in body weight effects.[176]

Numerous studies show that many tobacco consumers use tobacco to control their weight. For example, in two surveys, between one-third and one-half of young people reported that controlling weight was one of their reasons for smoking.[177]

An extensive discussion of the physiological and central nervous system effects of nicotine is available in the 1988 Surgeon General's Report.[178]

Thus, aside from addiction, there are other foreseeable pharmacological effects of nicotine use that are important to users; that these effects are actual reasons for consumption is discussed in section II.B.3., below.

5. Cigarettes and Smokeless Tobacco Deliver Pharmacologically Active Doses of Nicotine

Currently marketed cigarettes and smokeless tobacco deliver sufficient doses of nicotine to cause addiction and lead to other significant pharmacological effects that cause continued use of the products. This robust conclusion is supported by published research presented in section II.A., above, and thus is foreseeable to a reasonable tobacco manufacturer. For example, laboratory studies using commercial cigarettes demonstrate that the products contain pharmacologically active levels of nicotine; epidemiological data

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[176] Surgeon General's Report, 1988, at 431-432. *See* AR (Vol. 129 Ref. 1592).

[177] *Id.* at 438-440.

[178] *Id.* at 381-458.

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show that actual tobacco consumers do become addicted. Four additional types of evidence conclusively demonstrate that tobacco products deliver sufficient doses of nicotine: (1) measurements of blood nicotine levels after consumption of tobacco products; (2) laboratory studies using doses of nicotine that are equivalent to those imparted by tobacco use; (3) studies demonstrating that nicotine levels control tobacco consumption behavior (known as "compensation"); and (4) studies of nicotine replacement therapy.

Measurement of Blood Nicotine Levels. Evidence demonstrates that tobacco users receive pharmacological doses of nicotine when they consume cigarettes and smokeless tobacco. A currently marketed cigarette typically delivers about 1 mg of nicotine to the bloodstream of a smoker,[179] with individual intake ranging from 0.3 to 3.2 mg of nicotine per cigarette.[180] Studies have also revealed that, with regular use throughout the day, the levels of nicotine in the blood of smokeless tobacco users are similar to those observed in cigarette smokers. Data demonstrating that these products deliver substantial, pharmacologically active doses of nicotine are summarized in the Jurisdictional Analysis. *See* 60 FR 41571–41575.

Laboratory Studies. Long before evidence emerged that nicotine is addictive, studies demonstrated that the quantitative and even qualitative nature of the effects of

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[179] Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. *New England Journal of Medicine* 1994;331:123-125. *See* AR (Vol. 12 Ref. 130).

Gori GB, Lynch CJ. Analytical cigarette yields as predictors of smoke bioavailability. *Regulatory Toxicology and Pharmacology* 1985;5:314-326. *See* AR (Vol. 12 Ref. 142).

[180] Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. *New England Journal of Medicine* 1994;331:123-125. *See* AR (Vol. 12 Ref. 130).

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nicotine were dependent on the dose.[181] In the 1980's, particularly important discoveries provided indisputable proof that the nicotine dose levels produced by cigarette smoking affect the structure and function of the body, and that many of these effects are similar to those of prototypic addictive drugs. For example, nicotine, administered in doses considered biologically equivalent to those from tobacco use, was found to affect the brain's use of energy (cerebral glucose utilization).[182] Additionally, nicotine exposure at doses equivalent to those from tobacco use altered the brain so that excess nicotine receptors appeared on the surfaces of brain cells; this structural change was associated with altered responsiveness to nicotine.[183]

In addition, nicotine administered to animals in doses and at intervals comparable to those humans obtain from smoking produces one of the hallmark effects of addictive drugs: brain-mediated reinforcement of self-administration behavior. In the early 1980's, Goldberg and colleagues at Harvard and the National Institute on Drug Abuse provided unequivocal evidence that nicotine in doses comparable to those obtained in humans could

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[181] *See* Surgeon General's Report, 1988, chaps. 2-6. *See* AR (Vol. 129 Ref. 1592).

[182] *Id.* at 85-88.

[183] Marks MJ, Burch JB, Collins AC. Effects of chronic nicotine infusion on tolerance development and nicotine receptors. *Journal of Pharmacology and Experimental Therapeutics* 1983;226:817-825. *See* AR (Vol. 41 Ref. 103).

Surgeon General's Report, 1988, at 53-54. *See* AR (Vol. 129 Ref. 1592).

Id. at 32-33.

Benwell MEM, Balfour DJK, Anderson JM. Evidence that tobacco smoking increases the density of (–)-[^{3}H]nicotine binding sites in human brain. *Journal of Neurochemistry* 1988;50:1243-1247. *See* AR (Vol. 136 Ref. 1570).

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function powerfully to engender repetitive drug-seeking behavior in monkeys.[184] In the late 1980's, Corrigall and Coen developed a rat model utilizing key dosing parameters of cigarette smoking and smokeless tobacco use. This model provided for the delivery of very rapid and small doses and led the animals to repeatedly administer nicotine to themselves.[185]

Nicotine Control of Tobacco Use. Nicotine's key pharmacological role in actual tobacco products is also confirmed by evidence that tobacco users adjust their consumption based on the products' nicotine levels. Manipulation of nicotine levels in cigarettes while holding the tar content constant has shown that nicotine is responsible for the maintenance of cigarette smoking behavior. Cigarette smokers given cigarettes with a high nicotine content decrease the number of cigarettes smoked.[186] Modifying the amount of nicotine available by varying the length of cigarette smoked will influence the amount of the cigarette smoked[187] and the characteristics of smoking (e.g., number of puffs, puff duration, puff size, depth of inhalation, amount of tobacco smoked).[188] When cigarettes are shorter,

[184] Goldberg SR, Spealman RD, Goldberg DM, Persistent behavior at high rates maintained by intravenous self-administration of nicotine, *Science* 1981;214:573-575. *See* AR (Vol. 5 Ref. 35-2).

[185] Corrigall WA, Coen KM, Nicotine maintains robust self-administration in rats on a limited access schedule, *Psychopharmacology* 1989;99:473-478. *See* AR (Vol. 347 Ref. 5495).

[186] Goldfarb T, Griz ER, Jarvik ME, *et al.*, Reactions to cigarettes as a function of nicotine and "tar," *Clinical Pharmacology and Therapeutics* 1976;19:767-772. *See* AR (Vol. 39 Ref. 53).

[187] Jarvik ME, Popek P, Schneider NG, *et al.*, Can cigarette size and nicotine content influence smoking and puffing rates? *Psychopharmacology* 1978;58:303-306. *See* AR (Vol. 41 Ref. 86).

[188] Surgeon General's Report, 1988, at 158-163. *See* AR (Vol. 129 Ref. 1592).

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people smoke more of them.[189] Nemeth-Coslett and Griffiths showed that puff duration and puff volume are inversely proportional to the length of the cigarette.[190]

Studies conducted by Stolerman,[191] Nemeth-Coslett *et al.*,[192] and Pomerleau *et al.*[193] provide convincing evidence that tobacco products provide pharmacologically active doses of nicotine. Pretreatment of cigarette smokers with mecamylamine, an antagonist to nicotine that enters the brain, produced a dose-dependent increase in cigarette smoking (i.e., increases in puffs per cigarette, puff duration, and cigarettes per session and decreases in intercigarette interval and interpuff interval) that resembled what one would expect to see if the nicotine dose in the cigarette had been decreased. An increase in nicotine plasma levels also accompanied the increase in cigarette consumption. Pretreatment with another nicotine antagonist that did not enter the brain had no such effects. These studies clearly demonstrate that obtaining a pharmacologically active dose of nicotine in the brain motivates the amount of tobacco consumed on a daily basis.

Evidence from Nicotine Replacement Products. As described in the Jurisdictional Analysis, 60 FR 41565–41566, the ability of nicotine nasal spray to produce some of the classic characteristics of addiction to nicotine supports the position that tobacco users

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[189] Jarvik ME, Popek P, Schneider NG, *et al.*, Can cigarette size and nicotine content influence smoking and puffing rates? *Psychopharmacology* 1978;58:303-306. *See* AR (Vol. 41 Ref. 86).

[190] Surgeon General's Report, 1988, at 161. *See* AR (Vol. 129 Ref. 1592).

[191] Stolerman IP, Goldfarb T, Fink R, *et al.*, Influencing cigarette smoking with nicotine antagonists. *Psychopharmacologia* 1973;28:247-259. *See* AR (Vol. 42 Ref. 149).

[192] Nemeth-Coslett R, Henningfield JE, O'Keffe MK, *et al.*, Effects of mecamylamine on human cigarette smoking and subjective ratings, *Psychopharmacology* 1986;88:420-425. *See* AR (Vol. 41 Ref. 108).

[193] Pomerleau CS, Pomerleau OF, Majchrzak MJ, Mecamylamine pretreatment increases subsequent nicotine self-administration as indicated by changes in plasma nicotine level, *Psychopharmacology* 1987;91:391-393. *See* AR (Vol. 42 Ref. 112).

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seek nicotine primarily for its systemic pharmacological effects and not for its acute sensory effects. In contrast to cigarette smoke, aqueous nicotine spray does not provide the user any pleasing sensory characteristics. In fact, the spray can be irritating and unpleasant to use, and excessive use can cause ulcerations of the nasal mucosa. Notwithstanding the unpleasantness of the nicotine delivery mechanism and the presence of painful ulcerations that were further aggravated by its continued use, the spray was used to maintain nicotine dependence for some participants in clinical trials submitted to FDA.[194]

Studies of nicotine replacement therapies also demonstrate efficacy in maintaining abstinence from smoking.[195] The ability of nicotine to promote abstinence, even when delivered through the skin, without any taste or flavor, demonstrates its key role as a reinforcer of tobacco consumption. Based on these data, among others, organizations with expertise in pharmacology and addiction have determined that cigarettes and smokeless tobacco deliver pharmacologically active doses of nicotine. In the 1986 analysis of smokeless tobacco, the Surgeon General determined that smokeless tobacco use can be addictive.[196] In 1988, after an even more extensive consideration of the potential addictiveness of nicotine, the Surgeon General determined that: (1) "cigarettes and other forms of tobacco are addicting;" (2) "nicotine is the drug in tobacco that causes

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[194] FDA Drug Abuse Advisory Committee Background Information (Aug. 1, 1994). Joint Abuse Liability Review of Nicotine Nasal Spray. *See* AR (Vol. 9 Ref. 117).

[195] *See* appendix 1 to Jurisdictional Analysis. *See* AR (Vol. 1 Appendix 1).

[196] Department of Health and Human Services, Public Health Service, *The Health Consequences of Using Smokeless Tobacco: A Report of the Advisory Committee to the Surgeon General, 1986*, NIH Publication No. 86-2874 (Bethesda MD: DHHS, PHS, 1986) (hereinafter cited as Surgeon General's Report, *Smokeless Tobacco*, 1986), at viii. *See* AR (Vol. 128 Ref. 1591).

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addiction;" and (3) "the pharmacological and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine."[197] On August 2, 1994, FDA's Drug Abuse Advisory Committee, an independent group composed primarily of experts on addiction science, concluded that nicotine as delivered by commonly used tobacco products can produce strong physiological effects, including addiction.[198]

6. Conclusion

Nicotine is addictive and produces foreseeable psychoactive and pharmacological effects in a substantial proportion of tobacco users. This conclusion is so robust—and the evidence for it is so voluminous—that every major public health organization and relevant scientific authority in the world is in agreement. It is FDA's responsibility to base its regulatory actions on well-founded and accepted scientific facts. In this case, FDA believes that a very strong scientific basis exists on which to conclude that it is foreseeable that nicotine will produce pharmacological effects in a substantial number of tobacco consumers and that those consumers will use tobacco products to satisfy their addiction and to obtain the other pharmacological effects of nicotine. To conclude otherwise would not be credible.

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[197] Surgeon General's Report, 1988, at 13-17. *See* AR (Vol. 129 Ref. 1592).

[198] Transcript to the FDA Drug Abuse Advisory Committee, Meeting 27, "Issues Concerning Nicotine-Containing Cigarettes and Other Tobacco Products" (Aug. 2, 1994), at 336-342. *See* AR (Vol. 255 Ref. 3445).

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7. Response to Additional Comments

a. Comments on the Professional Consensus That Nicotine Is Addictive

1. More than 150 professional health organizations or chapters, representing over 600,000 individuals and organizations, commented on whether nicotine is addictive. Virtually all concluded that it is. These groups include the following:

- The American Cancer Society
- The American College of Physicians
- The American Heart Association
- The American Lung Association
- The American Medical Association
- The American Psychiatric Association
- The American Psychological Association
- The American Society of Addiction Medicine
- The College on Problems of Drug Dependence
- The Society of General Internal Medicine
- The Society for Head and Neck Surgeons
- The Society for Research on Nicotine and Tobacco
- The Virginia Society of Hospital Pharmacists

FDA also notes that, of the more than 1,100 physicians, pharmacists, and other health professionals who commented on whether nicotine is addictive, virtually all agreed that it is.

The Agency concurs with the unanimous conclusion of these organizations, most of which have expertise in this area. FDA notes that organizations with vast experience

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examining other addictive drugs reached the same conclusion as organizations with vast experience studying nicotine. The former organizations include the American Psychiatric Association, the American Society of Addiction Medicine, the National Institute on Drug Abuse, and the World Health Organization. The latter include the American College of Chest Physicians and the Surgeon General's expert committees on tobacco.

2. The tobacco industry disputes the process by which the American Psychiatric Association concluded that nicotine is addictive. The industry quotes several critical comments about the *Diagnostic and Statistical Manual* to suggest that the entire DSM structure of classifying all psychiatric diagnoses is flawed. This position, held by a small minority of psychiatrists, has been decisively rejected by the profession as a whole. The DSM-IV is now used throughout the world to classify psychiatric disorders, including drug dependence.

FDA notes that, aside from this argument against the American Psychiatric Association, the industry does not dispute the expertise or decision-making capabilities of any of the other medical authorities originally cited by FDA. These authorities—which unanimously have concluded that nicotine is addictive—include the U.S. Surgeon General, the World Health Organization, the American Medical Association, the American Psychological Association, the Royal Society of Canada, and the Medical Research Council of the United Kingdom.

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b. Comments on the Definition of Addiction

1. Several tobacco industry comments argue that cigarettes and smokeless tobacco are not addictive under a now-discarded definition of addiction developed in the 1950's and used by the U.S. Surgeon General in 1964.

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FDA disagrees with these comments. First, the tobacco industry borrows only selectively from the 1950's definition of addiction, emphasizing only certain criteria from that definition. Second, while the scientific community has rejected this historical definition in part because it failed to clearly classify cocaine and amphetamines as addictive, *see* section II.A.3.b., above, subsequent evidence has shown that nicotine would now qualify as addictive *even by this outdated definition.* The criteria cited by the Surgeon General,[199] which were not met by nicotine on the basis of data available in the early 1960's, are all met on the basis of data available today. These include the following:

- Surgeon General's 1964 conclusion: No overpowering compulsion to use the drug.

  Subsequent data: Ample documentation exists today that persons dependent upon cocaine, heroin, or alcohol find it as difficult to abstain from tobacco as from these other drugs and that persons who know that their lives are in imminent danger from smoking nevertheless continue to smoke.[200]

- Surgeon General's 1964 conclusion: No tendency to increase the dose.

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[199] Department of Health, Education, and Welfare, Public Health Service, *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service* (Washington DC: GPO, 1964), at 349-352. *See* AR (Vol. 43 Ref. 156).

[200] Henningfield JE, Cohen C, Slade JD, Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991;86:565-569. *See* AR (Vol. 277 Ref. 3904).

Kozlowski LT, Wilkinson DA, Skinner W, *et al.*, Comparing tobacco cigarette dependence with other drug dependencies. *Journal of the American Medical Association* 1989;261:898-901. *See* AR (Vol. 84 Ref. 350).

West R, Himbury S, Smoking habits after laryngectomy, *British Medical Journal* 1985;291:514-515. *See* AR (Vol. 6 Ref. 59).

Davison G, Duffy M, Smoking habits of long term survivors of surgery for lung cancer, *Thorax* 1982;37:331-333. *See* AR (Vol. 6 Ref. 58).

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Subsequent data: We now know that only about 10% of cigarette smokers are able to sustain a level of intake of five or fewer cigarettes per day. For example, one study found that 90% of people who smoke escalate to daily doses of five or more cigarettes.[201] Cigarettes are similar to morphine-like drugs in that, when either substance is readily available to the user, intake often escalates over a period of months or years and then stabilizes at a level that may vary little from day to day for many years.[202]

- Surgeon General's 1964 conclusion: No physical dependence on the effects of the drug.

  Subsequent data: The documentation that nicotine produces physical dependence has now been provided by scores of clinical treatment studies and laboratory studies with humans and animals.[203] There is a characteristic

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[201] Benowitz NL. Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. IILA).

Henningfield JE, Cohen C, Slade JD. Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991;86:565-569. *See* AR (Vol. 277 Ref. 3904).

[202] Jaffe JH. Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-573). *See* AR (Vol. 535 Ref. 96, vol. IILG).

[203] Henningfield JE, Cohen C, Slade JD. Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991;86:565-569. *See* AR (Vol. 277 Ref. 3904).

Kozlowski L.T, Wilkinson DA, Skinner W, *et al.*, Comparing tobacco cigarette dependence with other drug dependencies, *Journal of the American Medical Association* 1989;261:898-901. *See* AR (Vol. 84 Ref. 350).

Surgeon General's Report, 1988, at 145-240. *See* AR (Vol. 129 Ref. 1592).

Corrigall WA, Herling S, Coen KM, Evidence for a behavioral deficit during withdrawal from nicotine treatment. *Pharmacology Biochemistry and Behavior* 1989; 33:559-562. *See* AR (Vol. 139 Ref. 1626).

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tobacco withdrawal syndrome that has been recognized by leading medical organizations.[204]

- Surgeon General's 1964 conclusion: Detrimental effects on society are not well documented.

  Subsequent data: The detrimental effects on smokers themselves were recognized in 1964; however, it was not until the 1980's that the direct adverse effects of smoking upon nonsmokers and the fetuses of pregnant smokers were unequivocally documented.[205] Moreover, it is now recognized that nicotine has a severe adverse economic impact on many aspects of society.[206]

In addition to these four specific criteria, the Surgeon General in 1964 mentioned several other reasons for failing to categorize nicotine as addicting. These conclusions and the current data are as follows:

- Surgeon General's 1964 conclusion: Cigarette smokers did not become intoxicated.

Levin ED, Morgan MM, Galvez C. *et al.*, Chronic nicotine and withdrawal effects on body weight and food and water consumption in female rats, *Physiology and Behavior* 1987; 39:441-444. *See* AR (Vol. 278 Ref. 3932)

[204] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 244-245. *See* AR (Vol. 37 Ref. 8).

[205] Department of Health and Human Services, Office on Smoking and Health, *The Health Consequences of Involuntary Smoking: A Report of the Surgeon General* (Atlanta: DHHS, 1986) (hereinafter cited as Surgeon General's Report, *Involuntary Smoking*, 1986). *See* AR (Vol. 128 Ref. 1591).

[206] McGinnis JM, Foege WH, Actual causes of death in the United States, *Journal of the American Medical Association* 1993;270(18):2207-2212. *See* AR (Vol. 2 Ref. 15-1).

Hearing on Preventive Health: An Ounce of Prevention Saves a Pound of Cure, Before the Special Committee on Aging, U.S. Senate, 103d Cong., 1st Sess. 2 (May 6, 1993) (statement of Roger Herdman, Maria Hewitt, Mary Laschober on smoking-related deaths and financial costs: Office of Technology Assessment Estimates for 1990). *See* AR (Vol. 170 Ref. 2024).

Hodgson TA, Cigarette smoking and lifetime medical expenditures, National Center for Health Statistics, *Milbank Quarterly* 1992;70(1):81-125. *See* AR (Vol. 19 Ref. 22).

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Subsequent data: It is now well understood that nicotine can intoxicate, intoxication is a sign of nicotine overdose, and first-time users often become intoxicated.[207] The ability of nicotine to produce strong physiological and behavioral effects, including death at high doses, is no less than that of amphetamine or morphine.[208] In practice, intoxication is rarely evident in regular users because they have developed an extremely high level of tolerance to this effect of nicotine.[209]

- Surgeon General's 1964 conclusion: Subjective effects of nicotine itself were not well documented. The 1942 study by Johnston showing that intravenous nicotine could mimic the effects of smoking[210] was apparently given little weight because the study did not have the appropriate control conditions to rule out bias.

  Subsequent data: By the 1980's and 1990's, many properly controlled studies using nicotine delivered intravenously, intranasally, and by inhalation essentially confirmed Johnston's findings.[211]

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[207] Surgeon General's Report, 1988, at 593-594. *See* AR (Vol. 129 Ref. 1592).

[208] *Id.* at 272-274, 594.

[209] *Id.* at 593-595.

[210] Johnston LM, Tobacco smoking and nicotine. *Lancet* 1942;2:742. *See* AR (Vol. 278 Ref. 3947).

[211] *See, e.g.*, Jones RT, Farrell TR III, Herning RI, Tobacco smoking and nicotine tolerance, in *Self-Administration of Abused Substances: Methods for Study*, ed. Krasnegor NA, NIDA Research Monograph 20 (Rockville MD: National Institute on Drug Abuse, 1978), at 202-208. *See* AR (Vol. 41 Ref. 88).

Henningfield JE, Miyasato K, Jasinski DR, Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine, *Journal of Pharmacology and Experimental Therapeutics* 1985;234:1-12. *See* AR (Vol. 39 Ref. 69).

Pomerleau CS, Pomerleau OF, Euphoriant effect of nicotine in smokers, *Psychopharmacology* 1992;108:460-465. *See* AR (Vol. 87 Ref. 426).

Perkins KA, Grobe JE, Epstein LH, *et al.*, Chronic and acute tolerance to subjective effects of nicotine, *Pharmacology, Biochemistry and Behavior* 1993;45:375-381. *See* AR (Vol. 271 Ref. 3728).

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- Surgeon General's 1964 conclusion: No well-controlled demonstration that nicotine substitution could facilitate tobacco abstinence.

  Subsequent data: The absence of a nicotine-delivering medication effective in helping people to achieve abstinence was also noted in the 1964 report. There is now powerful evidence that products devoid of any tobacco constituent except nicotine are effective aids to smoking cessation and to providing relief of withdrawal symptoms.[212]

- Surgeon General's 1964 conclusion: Personality deficit criteria did not appear satisfied.

  Subsequent data: It was noted that not categorizing tobacco use as an addiction avoided the inference that smokers would be considered to have "serious personality defects" under the definition of addiction then in place. We now understand that many people who develop addictions to cocaine, heroin, alcohol, or nicotine have no documented underlying personality disorder. Rather, the major cause of addiction is

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Perkins KA, Grobe JE, Epstein LH, *et al.*, Effects of nicotine on subjective arousal may be dependent on baseline subjective state, *Journal of Substance Abuse* 1992;4:131-141. *See* AR (Vol. 348 Ref. 5516).

Sutherland G, Stapleton JA, Russell MAH, *et al.*, Randomised controlled trial of nasal nicotine spray in smoking cessation, *Lancet* 1992;340:324-329. *See* AR (Vol. 91 Ref. 527).

Sutherland G, Russell MA, Stapleton J, *et al.*, Nasal nicotine spray: a rapid nicotine delivery system, *Psychopharmacology* 1992;108:512-518. *See* AR (Vol. 91 Ref. 526).

[212] Fagerstrom KO, Sawe U, Tonnesen P, Therapeutic use of nicotine patches: efficacy and safety, *Journal of Drug Development* 1993;5:191-205. *See* AR (Vol. 76 Ref. 156).

Fiore MC, Smith SS, Jorenby DE, *et al.*, The effectiveness of the nicotine patch for smoking cessation: a meta-analysis, *Journal of the American Medical Association* 1994;271:1940-1947. *See* AR (Vol. 6 Ref. 64-1).

Fiore MC, Jorenby DE, Baker TB, *et al.*, Tobacco dependence and the nicotine patch, *Journal of the American Medical Association* 1992;268:2687-2694. *See* AR (Vol. 351 Ref. 5609).

Surgeon General's Report, 1988, at 208. *See* AR (Vol. 129 Ref. 1592).

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the presence of a psychoactive, reinforcing drug and adequate access to the drug to enable the development and sustenance of addiction.

Thus, it is virtually certain that tobacco use would be considered an addiction under the definition used by the Surgeon General in 1964. Indeed, FDA notes that a study sponsored by the tobacco industry in 1963 concluded that tobacco was addictive under the same definition used by the Surgeon General in 1964.[213]

2. The tobacco industry observes that definitions of addiction from several medical authorities are not identical, quotes several experts stating that whether tobacco is addictive depends on the definition of addiction, and presents excerpts from several scientific publications to suggest that no precise definition of addiction exists. The industry also argues that the use of the word "addiction" rather than "dependence" is political and claims that the modern definition of addiction is motivated by public health goals, morality, and lawsuits. The industry concludes that the modern definition of addiction is inappropriate for use in considering whether a product is a drug under the Act.

FDA disagrees. As discussed in section II.A.3.b., above, there is remarkable consensus among medical authorities around the world on the meaning of addiction. The subtle variations among written definitions reflect wording and emphasis, not significant differences in concepts; such variations are not surprising, given that medical organizations often write their own definitions of diseases and disease progression. International consistency on the meaning of addiction is demonstrated by the fact that all relevant

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[213] Knapp PH. Bliss CM. Wells H. Addictive aspects in heavy cigarette smoking. *American Journal of Psychiatry* 1963:119:966. *See* AR (Vol. 528 Ref. 97. appendix 16).

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scientific bodies have concluded that nicotine is addictive. Indeed, the tobacco industry fails to suggest any reason to believe that the current international understanding of nicotine as addictive will change in the future.

The industry's quoting of addiction experts on the importance of defining addiction is not an argument against FDA's position. It is axiomatic that whether nicotine is addictive depends on the definition of addiction. The industry fails, however, to show that nicotine would not be considered addictive under any of the current definitions of addiction.

The industry's use of an article from the *Journal of the American Medical Association* to show that the definition of addiction is imprecise is equally unpersuasive.[214] The article describes how a national panel was appointed in 1983 to try to settle variations in definitions relating to substance abuse. The panel surveyed dozens of experts from major scientific organizations and produced a consensus definition of addiction: "A chronic disorder characterized by the compulsive use of a substance resulting in physical, psychological, or social harm to the user and continued use despite that harm."[215] This definition again is entirely consistent with the modern definition of addiction relied on by FDA, not the tobacco industry's preferred version from the 1950's.

The industry selectively quotes from several scientific publications that discuss subtle arguments over the precise definition of addiction. But these debates occur within a

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[214] Rinaldi RC, Steindler EM, Wilford BB, *et al.*, Clarification and standardization of substance abuse terminology, *Journal of the American Medical Association* 1988:259(4):555-557. *See* AR (Vol. 535 Ref. 96 vol. III.L).

[215] *Id.*

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

broad understanding of addiction that has garnered overwhelming consensus. This understanding universally considers nicotine to be addictive.

FDA, like many scientific and public health authorities, uses "addiction" and "dependence" interchangeably. Regardless of the terminology used, the concept that nicotine has substantial pharmacological effects on the brains of users that cause people to use tobacco compulsively is the same. Furthermore, any implication that the modern scientific understanding of addiction is motivated by public health goals, morals, or lawsuits is mistaken. As discussed in section II.A.3.b., above, the tobacco industry's preferred definition was discarded on scientific grounds in 1964, 15 years before nicotine was first considered addictive.

Thus, there is no basis upon which to conclude that FDA's finding that nicotine is addictive—a conclusion with nearly universal scientific backing—is not useful in determining whether nicotine is a "drug" under the Act. The fact that nicotine meets all currently accepted scientific definitions of a dependence-producing drug and that these definitions include as a criterion psychoactive effects on the brain is highly relevant to the Agency's inquiry.

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c. *General Comments on Laboratory Evidence of Addictive Potential*

1. Comments from numerous health professionals and scientists agree with FDA that laboratory data in animals and humans provide compelling evidence that nicotine in cigarettes and smokeless tobacco is a pharmacologically active agent that causes addiction. For example, the American Medical Association stated that it "concurs with the scientific rationale and legal basis for the FDA proposed action," and that it "strongly supports the scientific basis regarding nicotine . . . and its essential role in maintaining demand for tobacco

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products." Similarly, the Coalition on Smoking OR Health—an organization representing the American Heart Association, American Lung Association, and American Cancer Society—carefully reviewed the Jurisdictional Analysis "for accuracy, objectivity, and completeness" and concluded that "the FDA documents represent the most comprehensive, objective and scientifically accurate analysis of the impact of nicotine containing cigarettes and smokeless tobacco on the body ever conducted."

2. The tobacco industry repeatedly comments that evidence from one laboratory test *by itself* is not enough to justify the conclusion that nicotine is addictive. For example, the industry argues that positive results in drug discrimination tests in animals are not sufficient to prove that nicotine is addictive, as some nonaddictive substances also test positive. The industry repeats this same argument for subjective effects testing and animal self-administration studies. On several occasions, the industry uses quotations from addiction experts to support these arguments.

FDA agrees that evidence from each test *alone* may not prove conclusively that nicotine is addictive. But addiction authorities around the world determine whether a substance is addicting by considering results from all of the tests *together*. Nicotine tests positive in animal and human drug discrimination tests, subjective effects tests, and animal and human self-administration tests. Considering such evidence, the scientific community has overwhelmingly concluded that nicotine is addictive.

The tobacco industry's selective use of quotations from addiction experts illustrates the point. On several occasions, the industry tries to make it appear that the individuals quoted believe that addiction testing methods are not reliable or that nicotine is not addictive. In fact, these individuals are on record as reaching the opposite conclusions. For example, the

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tobacco industry selectively quotes from the work of Balster that "[t]he results of self-administration studies should not be used alone for evaluating abuse potential. A number of drugs which probably possess minimal or no abuse potential have been shown to function as reinforcers in preclinical drug self-administration studies."[216] The industry also culls a quote from Woods that "[i]t should be clear that the proposition, *viz.*, that the drugs that serve as reinforcers in animals are abused by humans, is greatly oversimplified."[217] In both cases, however, the authors believe that demonstrating that a drug tests positive in both self-administration studies *and* drug discrimination studies is sufficient evidence of its abuse liability.[218] Nicotine has repeatedly proved positive in both tests.

d. Comments on Tests of Psychoactivity

1. The tobacco industry disputes FDA's analysis of drug discrimination tests in animals. The industry argues that the purpose of drug discrimination studies is merely to demonstrate that the test subject "recognizes" or "identifies" a substance that has been administered. The industry further claims that laboratory animals have been able to

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[216] Balster RL. Drug abuse potential evaluation in animals. *British Journal of Addiction* 1991;86:1549-1558, at 1555. *See* AR (Vol. 8 Ref. 89).

[217] Woods J. Some thoughts on the relations between animal and human drug-taking. *Progress in Neuro-psychopharmacology and Biological Psychiatry* 1983;7:577-584, at 582. *See* AR (Vol. 535 Ref. 96, vol. III.N).

[218] Balster RL. Drug abuse potential evaluation in animals. *British Journal of Addiction* 1991;86:1549-1558, at 1555. *See* AR (Vol. 8 Ref. 89).

Woods J. Some thoughts on the relations between animal and human drug-taking. *Progress in Neuro-psychopharmacology and Biological Psychiatry* 1983;7:577-584, at 582. *See* AR (Vol. 535 Ref. 96, vol. III.N).

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discriminate nicotine in the studies cited by FDA because researchers used amounts of nicotine that vastly exceed the nicotine yields in commercial cigarettes.

FDA disagrees. Drug discrimination studies are not just a measure of whether or not the subject can "recognize" or "identify" a substance; these studies assess the psychoactivity of a drug. Drugs that can be successfully discriminated from placebo are psychoactive.[219]

FDA also disagrees that animals can discriminate nicotine's stimulus properties only when receiving doses that vastly exceed those absorbed by human smokers. It is misleading to make a direct comparison between the training dose administered to animals and the nicotine yields of commercial cigarettes. Pharmacological effects elicited by a drug are the result of its plasma concentration and the amount of drug at the receptor site (i.e., site of action), not necessarily of how much drug is in the product or the amount of drug administered per kilogram of body weight. This distinction becomes critical when comparing animals with different abilities to metabolize drugs. The same amount of drug per kilogram administered to two species may lead to radically different plasma concentrations, for example, if one species breaks down and excretes the drug faster than the other.

A study by Pratt *et al.*[220] cited by the comment actually demonstrates that doses of nicotine that can be discriminated by rats yield a plasma concentration of nicotine that is comparable to the plasma concentration of nicotine in human smokers. Accordingly, rats *can* learn to discriminate a dose of nicotine physiologically comparable to the dose received by

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[219] Surgeon General's Report. 1988, at 170-171. *See* AR (Vol. 129 Ref. 1592).

[220] Pratt JA, Stolerman IP, Garcha HS, *et al.*, Discriminative stimulus properties of nicotine: further evidence for mediation at a cholinergic receptor, *Psychopharmacology* 1983;81:54-60. *See* AR (Vol. 8 Ref. 90-2).

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cigarette smokers and smokeless tobacco users. Two studies by Stolerman *et al.*[221] also demonstrated that rats can discriminate from saline a dose of nicotine that is comparable to the dose delivered to human tobacco users.

2. The tobacco industry argues that nicotine's action as a discriminative stimulus is not exactly the same as that of cocaine and amphetamine.

It is well known that nicotine does not behave identically to cocaine and amphetamine in drug discrimination experiments. This difference does not mean that nicotine is not an addictive drug, however. Amphetamine, morphine, alcohol, and nicotine can all be differentiated from one another by animals and humans because of their unique effects. The fact that nicotine is not identical to cocaine is no more relevant than the fact that cocaine is not identical to morphine. What is critical is that all of these drugs are psychoactive because of their effects on the brain. The published data have shown that there are qualitative differences in these drugs' discriminative stimulus effects and that nicotine produces effects more amphetamine-like than morphine-like in animals and humans.[222] Thus, while nicotine's discriminative stimulus effects are unique, they resemble the effects of stimulants more closely than those of sedatives. These data confirm that nicotine produces critical discriminative and subjective effects shared by dependence-producing drugs.

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[221] Stolerman IP, Garcha HS, Pratt JA, *et al.*, Role of training dose in discrimination of nicotine and related compounds by rats, *Psychopharmacology* 1984;84:413-419. *See* AR (Vol. 8 Ref. 90-5).

Stolerman IP, Discriminative stimulus effects of nicotine in rats trained under different schedules of reinforcement, *Psychopharmacology* 1989;97:131-138. *See* AR (Vol. 9 Ref. 90-6).

[222] Pratt JA, Stolerman IP, Garcha HS, *et al.*, Discriminative stimulus properties of nicotine: further evidence for mediation at a cholinergic receptor, *Psychopharmacology* 1983;81:54-60. *See* AR (Vol. 8 Ref. 90-2).

Stolerman IP, Garcha HS, Pratt JA, *et al.*, Role of training dose in discrimination of nicotine and related compounds by rats, *Psychopharmacology* 1984;84:413-419. *See* AR (Vol. 8 Ref. 90-5).

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3. The tobacco industry contests FDA's interpretation of three studies on drug discrimination in humans cited in the Jurisdictional Analysis. The industry concludes that there is no evidence to suggest that nicotine functions as a discriminative stimulus in humans.

Upon review of these studies and the administrative record, FDA concludes that there is convincing evidence that nicotine tests positive in human drug discrimination studies. The industry disputes the conclusion that a study by Kallman *et al.* proved that discrimination occurred in the central nervous system.[223] FDA, however, never drew this conclusion. FDA cited this study to demonstrate that smokers can differentiate between high- and low-nicotine cigarettes, a finding conceded by the industry. Much other evidence in the administrative record, described in section II.A.3.c.i. of this document and in the 1988 Surgeon General's report,[224] demonstrates that the discrimination occurs in the central nervous system.

The industry also claims that a study by Perkins *et al.* did not demonstrate discrimination.[225] Noting that male subjects identified 2 ug/kg of nicotine (administered by nasal spray) versus placebo correctly 50% of the time, the industry claims that this is exactly the percentage that would do so by chance. The industry concludes that the drug discrimination demonstrated by this study was due purely to chance and was not due to any effects of nicotine in the brain.

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[223] Kallman WM, Kallman MJ, Harry GJ, *et al.*, Nicotine as a discriminative stimulus in human subjects, in *Drug Discrimination: Applications in CNS Pharmacology*, eds. Colpaert FC, Slangen JL (Amsterdam: Elsevier Biomedical Press, 1982), at 211-218. *See* AR (Vol. 41 Ref. 89).

[224] Surgeon General's Report, 1988, at 176-178. *See* AR (Vol. 129 Ref. 1592).

[225] Perkins K, Grobe J, Scierka A, *et al.*, Discriminative stimulus effects of nicotine in smokers, in *International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II*, eds. Clarke PBS, Quik M, Thurau K, *et al.* (Basel: Birkhauser Verlag, 1994), at 111. *See* AR (Vol. 42 Ref. 111).

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Upon review of the Perkins study, FDA notes that the industry has seriously misinterpreted its results. The study's objective was to determine whether subjects could differentiate the low dose of 12 ug/kg of nicotine versus placebo, and its finding was that 100% of all subjects correctly identified nicotine at this dose at least 80% of the time. The authors concluded, "These findings indicate that humans are able to discriminate among low doses of nicotine."[226] (The dose of 12 ug/kg of nicotine is less than the typical dose of nicotine received from a cigarette.[227]) Having demonstrated this finding, the authors went on to test even smaller doses to determine the lowest dose of effective discrimination, that is, the dose at which subjects discriminated nicotine at least 50% of the time. That such a dose exists does not disprove nicotine's role as a discriminative stimulus, as implied by the tobacco industry; a minimal dose that cannot be differentiated from placebo exists for *all* psychoactive drugs.

Finally, the industry contends that a study by Goldfarb *et al.* [228] is not a formal "discrimination" study. The Goldfarb study was cited not as a discrimination study but to demonstrate that humans can differentiate between cigarettes with different nicotine yields, a conclusion conceded by the industry.

4. The tobacco industry argues that studies of the "subjective effects" of nicotine have vague methods and use subjects who are not representative of all smokers. These

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[226] *Id.* at 111.

[227] Perkins KA, Grobe JE, Epstein LH, *et al.*, Chronic and acute tolerance to subjective effects of nicotine. *Pharmacology, Biochemistry and Behavior* 1993;45:375-381. *See* AR (Vol. 271 Ref. 3728).

[228] Goldfarb TL, Gritz ER, Jarvik ME, *et al.*, Reactions to cigarettes as a function of nicotine and "tar." *Clinical Pharmacology and Therapeutics* 1976;19:767-772. *See* AR (Vol. 39 Ref. 53).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

The results from the study by Henningfield *et al.* demonstrate that nicotine, delivered by intravenous injection or by inhalation of tobacco smoke, produces similar subjective effects. These effects include dose-related elevation in the Morphine-Benzedrine Group Scale and the "liking" scale. There is no possibility that the subjects were responding to the "flavor" of nicotine or tar when they were able to discriminate nicotine injected intravenously. Nicotine produced results similar to those of other dependence-producing drugs (e.g., morphine, cocaine, and amphetamine) on the scales used in this study.

Furthermore, researchers who preceded and followed Henningfield obtained consistent findings. Researchers other than Henningfield *et al.*, using methods other than the MBG and the "liking" scale, also confirmed that nicotine produces positive subjective effects after intranasal and intravenous administration.[232] Subjects in these studies used the following adjectives to describe the positive subjective effects of nicotine: "head rush," "feeling good," or "high." This evidence strongly demonstrates that nicotine—and not tar—is responsible for the "subjective effects" of cigarettes.

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[232] Sutherland G, Stapleton JA, Russell MAH, *et al.*, Randomised controlled trial of nasal nicotine spray in smoking cessation. *Lancet* 1992;340:324-329. *See* AR (Vol. 91 Ref. 527).

Sutherland G, Russell MA, Stapleton J, *et al.*, Nasal nicotine spray: a rapid nicotine delivery system, *Psychopharmacology* 1992;108:512-518. *See* AR (Vol. 91 Ref. 526).

Perkins KA, Grobe JE, Epstein LH, *et al.*, Chronic and acute tolerance to subjective effects of nicotine. *Pharmacology, Biochemistry and Behavior* 1993;45:375-381. *See* AR (Vol. 271 Ref. 3728).

Perkins KA, Grobe JE, Epstein LH, *et al.*, Effects of nicotine on subjective arousal may be dependent on baseline subjective state. *Journal of Substance Abuse* 1992;4:131-141. *See* AR (Vol. 348 Ref. 5516).

Johnston LM. Tobacco smoking and nicotine. *Lancet* 1942;2:742. *See* AR (Vol. 278 Ref. 3947).

Jones RT, Farrell TR III, Herning RI. Tobacco smoking and nicotine tolerance. in *Self-Administration of Abused Substances: Methods for Study*, ed. Krasnegor NA. NIDA Research Monograph 20 (Rockville MD: National Institute on Drug Abuse, 1978), at 202-208. *See* AR (Vol. 41 Ref. 88).

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Finally, the industry cites a study by Butschky *et al.*[233] to suggest that nicotine-free cigarettes cause "liking" too. What the industry does not mention is that the study was conducted in newly abstinent smokers and that these nicotine-free cigarettes were "liked" only when compared to lettuce cigarettes that the researchers acknowledged to be unpalatable. As described in section II.B.3., below, the repeated association of pharmacological effects and sensory effects over thousands of repetitions causes the sensory aspects of addictive behaviors (such as taste) to come to be associated with the pharmacological effect (such as "liking") of addictive substances. Much as Pavlov's dog salivated at the sound of the bell (a conditioned response), individuals addicted to drugs actually experience some of the effects of the psychoactive drug by conditioned cues associated with the act of self-administering the drug in the early stages of abstinence.[234] This phenomenon has been described for many drugs, including heroin.[235] Just as a heroin addict may experience a rush simply by injecting a saline solution, a cigarette smoker may experience pleasure when smoking a denicotinized cigarette. Thus, the finding that a denicotinized cigarette can trigger "liking" during withdrawal does not call into question the conclusion that nicotine has "subjective effects" in humans.

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[233] Butschky MF, Bailey D, Henningfield JE, *et al.*, Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers, *Pharmacology, Biochemistry and Behavior* 1995;50(1):91-96. *See* AR (Vol. 442 Ref. 7484).

[234] O'Brien CP, Testa T, Ternes J, *et al.*, Conditioning effects of narcotics in humans, in *Behavioral Tolerance: Research and Treatment Implications*, NIDA Research Monograph 18 (Washington DC: Government Printing Office No. 017-024-00899-8, Jan. 1978), at 67-71. *See* AR (Vol. 535 Ref. 96, vol. III.L).

[235] Surgeon General's Report, 1988, at 308-311. *See* AR (Vol. 129 Ref. 1592).

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e. Comments on Self-Administration and Reinforcement

1. The tobacco industry argues that nicotine's reinforcing effects are different from those of heroin and cocaine, that animals need to be trained to self-administer nicotine, that the reinforcing efficacy of nicotine is more like that of caffeine, and that in one study cited by FDA a light stimulus associated with nicotine was required for self-administration. The industry concludes that animal self-administration studies do not support the finding that nicotine is addictive.

FDA disagrees. Upon review of the evidence in the administrative record, FDA notes that there are over ten studies demonstrating self-administration of nicotine by animals.[236] Only one of these is specifically contested by the tobacco industry. Furthermore, none of the industry's arguments seriously call into question FDA's finding that animals self-administer nicotine in a manner consistent with other addictive substances.

It is true that the reinforcing effects of nicotine do differ from those of cocaine and heroin; all dependence-producing drugs are not alike. In fact, FDA noted that the range of environmental conditions under which nicotine functions as a positive reinforcer appears more limited than for cocaine.[237] The limited conditions under which animals self-administer nicotine, however, closely correspond to the conditions of human tobacco use. That is, animals self-administer nicotine when it is given intermittently—in a fashion similar to nicotine delivery from cigarettes and smokeless tobacco.

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[236] *See* appendix 1 to Jurisdictional Analysis. *See* AR (Vol. I Appendix 1).

[237] *Id.*

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FDA agrees that animals can be trained to self-administer nicotine. This method is widely accepted as standard practice in self-administration testing in animals. What is important is that, under these conditions, nicotine is self-administered significantly more than placebo and in a manner consistent with other addictive substances.

The tobacco industry cites a review chapter in a textbook on psychopharmacology to suggest that caffeine and nicotine self-administration are similar. The review article cited focuses on whether caffeine is a drug of abuse and, while casually noting similarities between some data on nicotine and caffeine, does not purport to analyze the studies on nicotine at all.[238] Indeed, caffeine self-administration in animals is weak and sporadic.[239] FDA further notes that the chapter on nicotine in this same textbook unequivocally concludes that nicotine is addictive.[240]

Finally, FDA agrees that the study by Goldberg *et al.*[241] showed that squirrel monkeys self-administer nicotine most actively when associated with a light stimulus. The tobacco

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[238] Griffiths RR, Mumford GK. Caffeine—A drug of abuse?. in *Psychopharmacology: The Fourth Generation of Progress*, eds. Bloom FE, Kupfer DJ (New York: Raven Press, 1995), at 1699-1713. *See* AR (Vol. 535 Ref. 96, vol. III.E).

[239] Heishman SJ, Henningfield JE. Stimulus functions of caffeine in humans: relation to dependence potential. *Neuroscience and Biobehavioral Reviews* 1992;16:273-287. *See* AR (Vol. 79 Ref. 230).

Griffiths RR, Woodson PP. Reinforcing properties of caffeine: studies in humans and laboratory animals. *Pharmacology, Biochemistry and Behavior* 1988;29(2):419-427. *See* AR (Vol. 535 Ref. 96, vol. III.E).

Jaffe JH. Drug addiction and drug abuse. in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-573), at 524. *See* AR (Vol. 535 Ref. 96, vol. III.G).

[240] Henningfield JE, Schuh LM, Jarvik ME. Pathophysiology of tobacco dependence. in *Psychopharmacology: The Fourth Generation of Progress*, eds. Bloom FE, Kupfer DJ (New York: Raven Press, 1995), at 1715-1729. *See* AR (Vol. 39 Ref. 72).

[241] Goldberg SR, Spealman RD, Goldberg DM. Persistent behavior at high rates maintained by intravenous self-administration of nicotine. *Science* 1981;214:573-575. *See* AR (Vol. 5 Ref. 35-2).

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industry implies that this finding means that the light stimulus—not nicotine—was responsible for nicotine self-administration in this study. FDA disagrees. Rates of self-administration of nicotine with the light stimulus *were markedly higher than rates of self-administration of placebo* with the light stimulus. Indeed, the monkeys' self-administration of nicotine was so intense that it resembled cocaine use. Thus, the conclusion that nicotine was not self-administered is incorrect; the correct conclusion is that nicotine self-administration was most dramatic when associated with environmental cues that had been linked to nicotine injections.

2. The smokeless tobacco industry claims that its products provide a constant dose of nicotine, a regimen that animals did not self-administer. This claim is contrary to the evidence. As described in section II.D., below, moist snuff and chewing tobacco do not provide uniform release of nicotine from the products. In fact, each pinch of smokeless tobacco provides nicotine that is absorbed rapidly for the first 5 minutes; the rate of absorption then tapers off until the next pinch is consumed. This pattern of nicotine consumption is similar to the regimen that was self-administered by animals.

3. The tobacco industry criticizes the human self-administration study conducted by Henningfield *et al.*[242] on the grounds that the number of subjects used in the study was too small, that the study should have been conducted with subjects without a history of drug abuse, and that the subjects also self-administered saline.

FDA believes that the study's design was sound and that the results are reliable. The procedure utilized by these researchers is the standard procedure utilized by all investigators evaluating the abuse liability of a compound in humans. This well-

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[242] Henningfield JE, Miyasoto K, Jasinski DR. Cigarette smokers self-administer intravenous nicotine. *Pharmacology, Biochemistry and Behavior* 1983;19:887-890. *See* AR (Vol. 39 Ref. 71).

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established procedure has been used to examine the abuse potential of a variety of compounds, such as alcohol, marijuana, heroin, and sedatives, in both inpatient and outpatient settings. In the evaluation of a new molecular entity (NME) that shows some structural and/or pharmacological similarities to known drugs of abuse, FDA requires that studies similar to this one be conducted in order to reach a regulatory decision on the abuse potential of the NME being considered for drug approval.[243]

In response to the concerns of the tobacco industry about the study methodology, the sample size of six is acceptable and the use of volunteers with histories of drug abuse is a valid method of conducting such research, according to the National Institute on Drug Abuse.[244] Human studies evaluating the abuse potential of a compound in subjects without a history of drug abuse do not produce valid results. Such tests in non-drug abusers could lead to the conclusion that drugs, including heroin, have a low potential to produce dependence because first-time users may not find them pleasant.[245]

With respect to the self-administration of saline, the comment overlooks major distinctions between nicotine and saline: (1) "subjective effects" were not associated with the saline deliveries, thus saline was not psychoactive; (2) in comparison to the orderly pattern of self-administration observed with the nicotine injections, the pattern of saline deliveries was highly variable; (3) the number of self-administered saline injections

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[243] *See* Surgeon General's Report, 1988, at 270. *See* AR (Vol. 129 Ref. 1592).

[244] Jasinski DR, Henningfield JE, Human abuse liability assessment by measurement of subjective and physiological effects, in *Testing for Abuse Liability of Drugs in Humans*, eds. Fischman MW, Mello NK, NIDA Research Monograph 92 (Rockville MD: National Institute on Drug Abuse, 1989). *See* AR (Vol. 76 Ref. 172).

[245] Jaffe JH, Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-573), at 529. *See* AR (Vol. 535 Ref. 96, vol. III.G).

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decreased across sessions while nicotine injections were constant in those subjects who were tested repetitively with saline and nicotine; and (4) when saline and nicotine were simultaneously available in a follow-up study, the volunteers self-administered nicotine almost exclusively and not saline.[246] Thus, saline was not psychoactive and did not function as a "positive reinforcer."

4. The tobacco industry argues that caffeine, rapid eye movement (REM) sleep, magnetic fields, and stress increase dopamine levels in the brain. According to the industry, then, nicotine's effect on dopamine activity is shared by several other compounds or experiences.

This argument is based on a mischaracterization of the relationship between addictive substances and dopamine activity. FDA found that nicotine and other addictive substances do more than increase dopamine levels in the brain; they increase dopamine activity in a specific system that signals reward and pleasure, thus leading to reinforcing behavior. Nicotine's effect in this system is similar to that of other dependence-producing substances. These conclusions are based on reproducible studies and are widely accepted in the scientific community. Indeed, none of the industry's cited studies casts any doubt on the profound effects of nicotine on this brain system.

One study, cited by the industry as proof of the effect of caffeine on dopamine levels, actually examined the effect of caffeine on aggressive behavior of rats. Dopamine levels were not even measured. The authors merely speculated at the end of the article

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[246] Surgeon General's Report, 1988, at 192. *See* AR (Vol. 129 Ref. 1592).

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that caffeine may affect rat aggression via dopamine. Moreover, they did not extend their speculation to reward or reinforcement.[247]

Another study, cited by the industry as proof of the effect of REM sleep and magnetic fields on dopamine, actually described two patients treated with magnetic fields—without any control group. The authors merely speculated that REM sleep deprivation and magnetic fields may affect dopamine in the mesolimbic system. But without a control group, it is impossible to assess whether there was *any* true response to magnetic fields.[248]

The industry cites a third study to suggest that stress increases dopamine levels.[249] This study delivered severe stimuli such as electric shocks to mice and studied dopamine responses. The authors concluded that a dopamine-based reward pathway exists and is altered under conditions of severe stress. This conclusion casts no doubt on the finding that nicotine also critically affects this pathway.

5. In a footnote, the tobacco industry argues that "it is not clear that nicotine's effects on dopaminergic mechanisms play a significant role in smoking behavior." This argument refers to a study by Corrigall and Coen.[250]

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[247] Petkov VV, Rousseva S, Effects of caffeine on aggressive behavior and avoidance learning of rats with isolation syndrome, *Methods and Findings in Experimental and Clinical Pharmacology* 1984;6(8):433-436. *See* AR (Vol. 535 Ref. 96, vol. III.L).

[248] Sandyk R, Tsagas N, Anninos PA, *et al.*, Magnetic fields mimic the behavioral effects of REM sleep deprivation in humans, *International Journal of Neuroscience* 1992;65(1-4):61-68. *See* AR (Vol. 535 Ref. 96, vol. III.L).

[249] Puglisi-Allegra S, Kempf E, Cabib S, Role of genotype in the adaptation of the brain dopamine system to stress, *Neuroscience and Biobehavioral Reviews* 1990;14(4):523-528. *See* AR (Vol. 535 Ref. 96, vol. III.L).

[250] Corrigall W, Coen K, Dopamine mechanisms play at best a small role in the nicotine discriminative stimulus, *Pharmacology, Biochemistry and Behavior* 1994;48(3):817-820. *See* AR (Vol. 535 Ref. 96, vol. III.B).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

FDA has reviewed the study in question and concludes that the tobacco industry's conclusion seriously misrepresents the research. In this paper, the authors suggested that dopamine activity may not explain why smokers recognize low doses of nicotine in their brain, but the authors never doubted that dopamine activity is essential to the reward associated with smoking. The same article cited by the industry includes the statement that "the reinforcing effects of nicotine have a dopaminergic substrate, likely the ascending mesolimbic dopamine system"[251]—exactly the finding of FDA. These researchers, misrepresented by the industry to suggest a small role for dopamine in smoking behavior, have demonstrated in their own laboratory that dopamine activity significantly affects nicotine consumption.[252]

f. Comments on Withdrawal, Tolerance, and Nicotine Replacement

1. The tobacco industry argues that the effects of withdrawal from nicotine are not substantial. This argument is based upon multiple overlapping and sometimes contradictory contentions: (1) nicotine withdrawal is not as severe as withdrawal from certain other drugs, and some people quit smoking easily; (2) physical and psychological symptoms experienced during nicotine withdrawal are not the same among all abstinent users; (3) withdrawal from nicotine produces psychological but not physical symptoms; (4) the psychological symptoms of abstinence may actually be a psychopathological condition previously suppressed by nicotine or may be frustration with losing a pleasurable activity; (5) what is thought to be nicotine withdrawal may actually be caffeine withdrawal

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[251] *Id.* at 817.

[252] Corrigall WA, Franklin KBJ, Coen KM, *et al.*, The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine, *Psychopharmacology* 1992;107:285-289. *See* AR (Vol. 8 Ref. 93-4).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

or caffeine toxicity; (6) the severity of withdrawal symptoms does not always correlate with relapse; and (7) epidemiological studies cited by FDA do not prove a substantial withdrawal syndrome.

Upon careful review of the industry's comments and the administrative record, FDA finds that nicotine clearly produces a withdrawal syndrome among abstinent tobacco users. This syndrome—which includes both psychological and physiological symptoms—is described in numerous scientific articles and reviews cited by FDA,[253] only a few of which were criticized by the tobacco industry. Of the studies on withdrawal from smokeless tobacco cited by FDA, none is contested by the industry. The tobacco industry also accepts FDA's finding that tobacco withdrawal causes many significant autonomic changes, such as changes in heart rate. Several of the industry's arguments do not seriously contest the fact that nicotine has a substantial withdrawal syndrome. The remaining arguments contradict each other. The Agency's specific responses to the major industry contentions are as follows:

- Nicotine withdrawal is not as severe as withdrawal from certain other drugs, and some people quit smoking easily.

FDA agrees that withdrawal from nicotine is not as acutely life-threatening as withdrawal from certain addictive drugs such as alcohol or short-acting barbiturates. But the severity of nicotine withdrawal *is* comparable to that of other addictive drugs such as

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[253] *See* Jurisdictional Analysis, 60 FR 41560–41562

See also Surgeon General's Report, 1988, at 197-207. *See* AR (Vol. 129 Ref. 1592).

American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 244-245. *See* AR (Vol. 37 Ref. 8).

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cocaine.[254] Medical authorities around the world have recognized the existence of a nicotine withdrawal syndrome that causes "clinically significant distress or impairment in social, occupational, or other areas of functioning."[255]

FDA agrees that some people quit tobacco products easily. Similarly, some people quit cocaine and other addictive substances easily.[256] However, for most addicted users of tobacco, quitting is very difficult. *See* section II.A.3.c.ii., above. The characteristic feature of an addictive substance is that it is difficult for most people to quit. Thus, the fact that some people can quit smoking easily is irrelevant to nicotine's addictiveness and to the scientific consensus supporting a nicotine withdrawal syndrome. Moreover, it may actually be easier to quit other powerful substances than to quit nicotine. Smokers who consume about a pack or more of cigarettes per day are more than twice as likely to report withdrawal symptoms during abstinence as people who consume five or more drinks on five or more occasions in a month, people who repeatedly use cocaine, and people who repeatedly use marijuana.[257]

- Physical and psychological symptoms experienced during nicotine withdrawal are not the same among all abstinent users.

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[254] Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437, at 429. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[255] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 245. *See* AR (Vol. 37 Ref. 8).

[256] Kleber H, Don't you believe that nicotine isn't addictive, *New York Times*, Apr. 4, 1994. *See* AR (Vol. 196 Ref. 2497).

Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437, at 429. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[257] Henningfield JE, Clayton R, Pollin W, Involvement of tobacco in alcoholism and illicit drug use, *British Journal of Addiction* 1990;85:279-292, at 280-281. *See* AR (Vol. 39 Ref. 66).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

FDA agrees that there is variation among tobacco users' physical and psychological responses to abstinence. But, as described in section II.A.3.c.i., above, and in reviews cited by the Agency, several symptoms are so common as to be part of a defined syndrome.[258] These symptoms include depressed mood, insomnia, irritability, anxiety, difficulty concentrating, restlessness, decreased heart rate, and increased appetite. Thousands of individuals around the world have reported these symptoms in studies of tobacco abstinence.

- Withdrawal from nicotine produces psychological but not physical symptoms.

The tobacco industry goes on to quote selectively from some researchers to suggest that nicotine withdrawal does not produce physical symptoms. This argument is at odds not only with the consensus understanding of nicotine withdrawal, but also with other quotations used by the tobacco industry in the same comment, which suggests that common withdrawal symptoms include, for example, "headache."[259]

Indeed, the very sources cited by the tobacco industry clearly agree with FDA's finding of a substantial tobacco withdrawal syndrome. For example, Balfour, who is quoted by the industry to suggest that withdrawal is mainly psychological, states that "many habitual smokers *experience significant and unpleasant withdrawal effects* when they first stop smoking which can be ameliorated by giving nicotine in another form."[260]

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[258] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 244-245. *See* AR (Vol. 37 Ref. 8).

[259] Clark WG, Brater DC, Johnson AR, Drug abuse and dependence, in *Goth's Medical Pharmacology* (Baltimore: Mosby), 336-352, at 347. *See* AR (Vol. 535 Ref. 96, vol. III.B).

[260] Balfour DJK, The neurochemical mechanisms underlying nicotine tolerance and dependence, in *The Biological Bases of Drug Tolerance and Dependence*, ed. Prau JA (New York: Academic Press, 1991), 121-151, at 123 (citation omitted) (emphasis added). *See* AR (Vol. 535 Ref. 96, vol. III.A).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

Similarly, a quotation culled from a review by Hughes *et al.* is used to support the conclusion that the effects of nicotine withdrawal are not substantial. In fact, Hughes *et al.* attribute multiple physical and psychological symptoms to nicotine withdrawal and conclude that some symptoms can be so severe that they may "prevent smoking cessation."[261]

- The psychological symptoms of abstinence actually may be a psychopathological condition previously suppressed by nicotine or may be frustration with losing a pleasurable activity.

The tobacco industry cites the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association for this assertion, but offers no evidence to suggest that any significant number of quitting smokers have psychiatric diagnoses or are just frustrated. Nor does the DSM. Its actual text merely alerts clinicians not to mistake symptoms of abstinence for psychopathology or frustration "in any given case."[262]

- What is thought to be nicotine withdrawal may actually be caffeine withdrawal or caffeine toxicity.

FDA agrees that some symptoms are common to caffeine and nicotine withdrawal, and some are common to nicotine withdrawal and caffeine toxicity. Withdrawal from nicotine and cocaine also causes common symptoms of depressed mood, increased

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[261] Hughes JR, Higgins ST, Hatsukami D. Effects of abstinence from tobacco: a critical review, *Research Advances in Alcohol and Drug Problems* 1990;10:317-398, at 381. *See* AR (Vol. 535 Ref. 96, vol. III.G).

[262] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 3d ed., revised (Washington DC: American Psychiatric Association, 1987), at 150. *See* AR (Vol. 535 Ref. 96, vol. III.A).

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appetite, and insomnia.[263] Such overlap has not led any credible scientific source to conclude that nicotine withdrawal has been confused with another drug's syndrome and therefore does not exist.

- The severity of withdrawal symptoms does not always correlate with relapse.

On several occasions in its comments, the tobacco industry claims that the severity of withdrawal does not directly predict relapse. Based on this observation, the industry concludes that the symptoms of withdrawal from tobacco are not significant and that physical dependence to nicotine is not real.

FDA disagrees. Severity of withdrawal does predict relapse; most people who quit smoking relapse within 1 week,[264] when withdrawal symptoms are at or near their peak.[265] Moreover, studies indicate that light smokers, who are less likely to suffer withdrawal symptoms, are more likely to succeed in quitting than are heavier smokers.[266]

The industry's argument is based on the mistaken assumption that, if withdrawal symptoms were significant, their presence would perfectly correlate with relapse. But, as described in depth in the 1988 Surgeon General's Report, multiple confounding factors are associated with relapse to use of *any* addictive substance, no matter how significant the withdrawal syndrome.[267] These factors include psychiatric impairment, expectations,

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[263] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association. 1994). *See* AR (Vol. 535 Ref. 96, vol. III.B).

[264] Hughes JR, Gulliver SB, Fenwick JW, *et al.*, Smoking cessation among self-quitters. *Health Psychology* 1992;11:331-334, at 333. *See* AR (Vol. 348 Ref. 5512).

[265] Hughes JR, Gust SW, Skoog K, *et al.*, Symptoms of tobacco withdrawal: a replication and extension. *Archives of General Psychiatry* 1991;48:52-59, at 56. *See* AR (Vol. 129 Ref. 1404).

[266] Surgeon General's Report, 1988, at 315-316. *See* AR (Vol. 129 Ref. 1592).

[267] *Id.* at 315-324.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

demographics, enrollment in treatment programs, peer influence, and social support. Even life-threatening withdrawal symptoms associated with drugs such as alcohol do not necessarily lead to relapse. After a complete review of available evidence, the Surgeon General concluded that nicotine's pharmacological role in relapse is similar to the role of opioids and alcohol.[268] Thus, the absence of a perfect correlation between withdrawal severity and the precise timing of a relapse does not compel the conclusion that withdrawal symptoms are insignificant or that physical dependence to nicotine is not real.

- Epidemiological studies cited by FDA do not prove a substantial withdrawal syndrome.

The tobacco industry criticizes several studies cited by FDA in support of a tobacco withdrawal syndrome. Upon review of these studies, FDA finds that the industry's comments take quotations out of context and make inappropriate inferences from researchers' findings. For example, the industry objects to a study by Hughes *et al.*[269] on the grounds that the researchers tabulated withdrawal symptoms on only 105 of the 315 subjects. In fact, the analysis of withdrawal appropriately included *every subject* in the study who was abstinent from both tobacco and nicotine. The other 210 subjects received nicotine gum to reduce their withdrawal symptoms; these subjects were thus inappropriate for research on the severity of withdrawal.

Similarly, the industry claims to provide data to contradict FDA's citation of the 1991 and 1992 National Household Surveys. But FDA's data reported the prevalence of withdrawal symptoms for smokers who consume sixteen to twenty-five cigarettes per day.

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[268] *Id.* at 323.

[269] Hughes JR, Gust SW, Skoog K, *et al.*, Symptoms of tobacco withdrawal: a replication and extension, *Archives of General Psychiatry* 1991:48:52-59. *See* AR (Vol. 129 Ref. 1404).

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The industry's data are based on a different set of smokers and, at any rate, are hardly different from FDA's.

Such arguments cannot seriously challenge the scientific consensus that led the American Psychiatric Association to define Tobacco Withdrawal Syndrome in 1980 and to ratify its decision again as recently as 1994 in DSM-IV.

2. The tobacco industry argues that nicotine does not induce pharmacological tolerance. This conclusion is based upon several arguments: (1) tolerance can be both pharmacological and nonpharmacological; (2) smokers and users of smokeless tobacco do not continue to increase their tobacco consumption over the course of their lives and thus do not escalate their dose; (3) FDA's studies on dose escalation are not persuasive; and (4) a study on low-nicotine snuff disproves tolerance.

FDA disagrees with the industry's analysis and conclusion. Much uncontested evidence in the administrative record demonstrates conclusively that nicotine causes tolerance in tobacco users. For example, the industry does not dispute evidence of diminished cardiovascular and nervous system responses to nicotine over the course of a day. Nor does the industry deny that many cigarette smokers escalate their doses of nicotine to daily use[270] or that the age of young consumers of smokeless tobacco correlates with the amount of use.[271] Furthermore, the arguments that the industry does make are not persuasive, as discussed below.

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[270] Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. III.A).

Henningfield JE, Cohen C, Slade JD, Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991;86:565-569. *See* AR (Vol. 277 Ref. 3904).

[271] World Health Organization, *Smokeless Tobacco Control: Report of a WHO Study Group*, WHO Technical Report Series No. 773 (Geneva: WHO, 1988), at 36. *See* AR (Vol. 7 Ref. 83).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

The industry's description of two kinds of tolerance is irrelevant. Sources in the administrative record cited by FDA refer exclusively to pharmacological tolerance. *See* sections II.A.3.c.i. and II.A.3.c.ii., above.

The tobacco industry makes the observation that smoking behavior reaches a plateau as the smoker grows older. Similarly, the smokeless tobacco industry points out that middle-aged users may consume less than young adults. But these observations do not disprove the existence of tolerance, which does not require forever-increasing consumption of a substance. Tolerance is a phenomenon that develops rapidly, leads the vast majority of beginning tobacco users to escalate their dose, and then can eventually result in a stable pattern of consumption. Some heroin addicts also eventually reach a level of consumption that may remain constant for years.[272]

The tobacco industry asserts that a study cited by FDA on the proportion of smokers who report needing more cigarettes to obtain desired effects does not support the idea of tolerance to nicotine and also does not prove that such tolerance is widespread or marked. FDA disagrees with these assertions. The industry cites no data or references to explain why the study does not demonstrate tolerance. In fact, the study's findings perfectly fit the tobacco industry's *own* definition of tolerance that "more drug is necessary to produce the desired effect." People who have tried cigarettes at least once are more likely to report the need for larger doses to get the same effect than people who have tried

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[272] Jaffe JH. Drug addiction and drug abuse. in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-573), at 531-532. *See* AR (Vol. 535 Ref. 96, vol. III.G).

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cocaine, marijuana, and alcohol at least once.[273] Moreover, FDA notes that epidemiological data are just one demonstration of tolerance; most of the evidence on tolerance to nicotine presented by FDA is uncontested by the tobacco industry.

Finally, the smokeless tobacco industry cites a study that measures the response of oral tobacco users to a low-nicotine snuff. In the study, users increased their consumption of tobacco to compensate for its lower nicotine content. The industry's argument here confuses tolerance with compensation. FDA addresses the industry's comments on compensation in section II.A.7.i., above.

3. The tobacco industry cites research on nicotine replacement therapies to argue that nicotine is not a key reason for tobacco use. According to the industry, if nicotine were central to tobacco consumption, providing nicotine replacement should eliminate smoking behavior and all withdrawal symptoms. The industry contends that nicotine replacement trials cited by FDA do not demonstrate either efficacy of replacement therapy or elimination of withdrawal symptoms. The industry disputes FDA's summary of nicotine replacement trials and makes multiple objections to individual studies. The industry also contends that the study population is not generalizable to the entire smoking population.

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Upon review of the industry's detailed comments and the data in the administrative record, FDA disagrees with the industry's position on nicotine replacement therapies. Scientific consensus supports the view that such therapies not only reduce withdrawal symptoms but increase abstinence. An extensive preapproval evaluation of such therapies

[273] Henningfield JE, Clayton R, Pollin W. Involvement of tobacco in alcoholism and illicit drug use. *British Journal of Addiction* 1990;85:279-292. *See* AR (Vol. 39 Ref. 66).

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by FDA also concluded that they were safe and effective, and even sources cited by the tobacco industry agree. The efficacy of nicotine replacement therapies is strong proof of the central role of nicotine in tobacco consumption. The industry's position is based upon mistaken assumptions, misinterpretation of clinical trials, and misuse of FDA reviews.

According to the tobacco industry, replacing one form of an addictive substance with another form should completely eliminate the addict's desire to use the substance. If this assumption were correct, then no methadone user would ever relapse to heroin. In fact, providing oral methadone in substance abuse clinics helps only some opioid users to remain totally abstinent,[274] and abstinence rates of former heroin users on methadone are similar to those of former smokers receiving nicotine replacement therapy.[275] The industry's simplistic formulation ignores many factors, such as the importance of the route and speed of drug administration. Just as a heroin addict may want a "rush" from injection and reject the steady dose of oral methadone, a tobacco user may prefer the "rapid, peaking" dose of inhaled nicotine over the more steady dose from replacement therapy.[276] Given the strength of addiction to tobacco products, it is noteworthy that there is a

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[274] Jaffe JH, Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-573), at 531-532. *See* AR (Vol. 535 Ref. 96, vol. III.G).

[275] Henningfield JE, Griffiths RR, Jasinski DR, Cigarette smoking and opioid dependence: common factors. Presented at the meeting of the American Psychological Association (Sep. 2, 1980). *See* AR (Vol. 80 Ref. 254).

Surgeon General's Report, *Smokeless Tobacco*. 1986, at 155. *See* AR (Vol. 128 Ref. 1591).

Gorelick D. Transcript to the FDA Drug Abuse Advisory Committee. Meeting 27, "Issues Concerning Nicotine-Containing Cigarettes and Other Tobacco Products" (Aug. 2, 1994), 292. *See* AR (Vol. 255 Ref. 3445).

[276] Research and Development/Quality, Transdermal Nicotine, at 3. *See* AR (Vol. 531 Ref. 124).

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significant increase in abstinence with replacement therapy, but it is not surprising that these products are not always effective.

The industry also argues that replacing an addictive substance with another form should eliminate all withdrawal symptoms. In fact, providing nicotine does dramatically reduce physiological withdrawal symptoms.[277] Psychological withdrawal is reduced but not eliminated, primarily because users have associated tobacco consumption with certain stimuli, such as taste and ritual. Such "conditioned" cues become part of the tobacco consumption experience, and the denial of such cues can lead to behavioral symptoms. In this sense, nicotine is like other addictive drugs.[278]

The industry misinterprets data on the efficacy of nicotine replacement therapies. First, the industry argues that FDA's data do not support the conclusion that the initial quit rate is "about 50%." The actual studies cited 1-month quit rates of 35%, 61%, 50%, 50%, 26%, 57%, 47%, and 36%. The overall average for all studies was 49%.[279]

Second, the industry argues that some individual studies do not show a statistically significant increased quit rate with nicotine replacement therapy. The Jurisdictional Analysis, however, included a chart showing the overwhelming consistency among nineteen studies on nicotine replacement therapies in demonstrating efficacy.[280]

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[277] Surgeon General's Report, 1988, at 208. *See* AR (Vol. 129 Ref. 1592).

[278] Benowitz NL, Cigarette smoking and nicotine addiction. *Medical Clinics of North America* 1992;76(2):415-437, at 418. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[279] *See* appendix 1 to Jurisdictional Analysis. *See* AR (Vol. I Appendix 1).

[280] *Id.*

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

A definitive meta-analysis on the efficacy of the nicotine patch was cited by FDA, and its methods and results were not disputed by the tobacco industry. This study, published in the *Journal of the American Medical Association*, reviewed seventeen studies involving *over 5,000* patients and concluded that "this meta-analysis provides *compelling evidence that the nicotine patch is a consistently effective aid to smoking cessation.* Individuals wearing the active nicotine patch were more than twice as likely to quit smoking as were individuals wearing a placebo patch."[281]

Third, the industry makes multiple objections to individual studies on nicotine replacement therapy. These objections dispute fine points of methodology and often cite FDA reviewers' own criticisms of the studies. To the extent that the industry heavily relies on FDA's critique of the studies, the industry should accept FDA's conclusion that the studies demonstrate the efficacy of nicotine replacement therapy. Indeed, FDA has not only the statutory authority but also the expertise to determine whether a new drug therapy is efficacious. After extensive premarket review, FDA concluded that nicotine replacement therapies are efficacious. FDA's conclusion is consistent with scientific consensus.

The tobacco industry also argues that the subjects in trials on nicotine replacement therapy are not representative of all smokers. But FDA's reason for citing the research was to demonstrate that providing nicotine by another means enhances abstinence and reduces withdrawal where it has been studied. These results show the critical

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[281] Fiore MC, Smith SS, Jorenby DE, *et al.*, The effectiveness of the nicotine patch for smoking cessation: a meta-analysis, *Journal of the American Medical Association* 1994;271:1940-1947, at 1945 (emphasis added). *See* AR (Vol. 6 Ref. 64-1).

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pharmacological role of nicotine in tobacco use. Indeed, if the tobacco industry were correct that nicotine's only important role in tobacco is for "flavor," then there should be absolutely no benefits in *any* study of transdermal nicotine replacement therapy. That nicotine replacement is effective is conclusive evidence of nicotine's role as a pharmacological reinforcer.

4. The tobacco industry argues that studies on nicotine replacement therapy cannot be relied upon to demonstrate that a high proportion of smokers are addicted.

FDA agrees with this comment. Other studies, cited in section II.B.2.a., below, however, do demonstrate that a high proportion of smokers are addicted.

g. Comments on Epidemiological Studies

1. The tobacco industry claims that studies of individual DSM criteria do not demonstrate that any group of smokers satisfied sufficient criteria to qualify for the diagnosis of addiction.

FDA cited these studies as support for the conclusion that a significant proportion of tobacco consumers are addicted to nicotine. This conclusion is primarily demonstrated by population-based studies, including the DSM-IV field trial, which show that the vast majority of smokers do meet sufficient DSM criteria to be considered nicotine dependent, discussed in more detail in section II.B., below. The field trial was a large, multicenter study conducted in 1991 and 1992 at five sites across the country (Burlington, VT; Philadelphia, PA; Denver, CO; St. Louis, MO; and San Diego, CA).[282] The population

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[282] Woody GE, Cotler LB, Cacciola J, Severity of dependence: data from the DSM-IV field trials, *Addiction* 1993;88:1573-1579. *See* AR (Vol. 13 Ref. 150).

Cotler L, Comparing DSM-*III*-R and ICD-10 substance use disorders, *Addiction* 1993;88:689-696. *See* AR (Vol. 13 Ref. 149).

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studied represented a diverse sample and included African-Americans, women, others randomly selected from the general population, and still others with a range of diagnoses and substance use patterns. The field trial documents that 80% to 87% of smokers studied qualified for the diagnosis of nicotine dependence. In its comments, the American Psychiatric Association concurs with the Agency's findings: "DSM based studies also found that 80% to 90% of adult smokers are nicotine dependent."[283]

The tobacco industry's comments on population-based studies are addressed in section II.B.4.b., below. It is relevant to mention here that, if the industry's assertion that these population-based studies are not representative of all smokers is correct, then large surveys of whether all smokers meet individual DSM criteria would show inconsistent results. But this is not the case. Overwhelming evidence, cited in section II.A.3.c.ii., above, conclusively demonstrates that the vast majority of tobacco consumers meet individual criteria for addiction.

2. The tobacco industry disputes that use of tobacco products persists longer and in greater amounts than the user intends. According to the industry, studies cited by FDA demonstrate that, at most, 30% of people who have ever tried tobacco become "dependent" by FDA's definition. The industry also argues that the desire to quit is not evidence of intent to cut down.

FDA disagrees with the industry's position. It is widely accepted that users of tobacco products consume more than they originally intended.[284] Longitudinal data, cited

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[283] American Psychiatric Association, Comment (Jan. 2, 1996), at 2. *See* AR (Vol. 700 Ref. 1020).

[284] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 243. *See* AR (Vol. 37 Ref. 8).

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in section II.A.3.c.ii., above, demonstrate that smokers frequently underestimate how much they will be smoking in the future. As many as 90% of current users smoke more than five cigarettes a day,[285] despite the evidence that nearly half of young consumers do not intend to become daily smokers.[286] Although estimates vary from study to study, persons who have smoked at least one cigarette are about twice as likely to develop dependence as are persons who have ever tried cocaine or alcohol.[287]

If an individual wants to quit smoking but cannot, then the individual is smoking more than he or she intends. The overwhelming evidence presented in section II.A.3.c.ii., above, that many would-be quitters cannot attain abstinence supports the contention that consumers use cigarettes longer and in greater amounts than intended.

3. The tobacco industry disputes that tobacco use continues despite attempts to quit. The industry observes that 90% of cigarette smokers who quit succeed by themselves, and the smokeless tobacco industry suggests that 75% of successful quitters find it easy to quit. The tobacco industry also alleges that FDA mischaracterizes data on self-reports of dependence from the National Household Surveys and misrepresents

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[285] Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. III.A).

Henningfield JE, Cohen C, Slade JD, Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991;86:565-569. *See* AR (Vol. 277 Ref. 3904).

[286] Elders MJ, Perry CL, Eriksen MP, *et al.*, The report of the Surgeon General: preventing tobacco use among young people, *American Journal of Public Health* 1994;84(4):543-547, at 544. *See* AR (Vol. 38 Ref. 39).

[287] Anthony JC, Warner LA, Kessler RC, Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from the National Comorbidity Survey, *Experimental and Clinical Psychopharmacology* 1994;2:244-268. *See* AR (Vol. 37 Ref. 4).

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abstinence failure rates from a CDC study. The industry further argues that smokers may lie on surveys about their desire to quit.

After reviewing industry comments and the administrative record, FDA concludes that there is overwhelming evidence that tobacco use continues despite attempts to quit. Indeed, this fact is well known to the tobacco industry. For example, Brown & Williamson's data show that, while *32 million* Americans attempted to quit each year from 1981 to 1983, fewer than a third were successful for 6 months. *See* Jurisdictional Analysis, 60 FR 41668. Philip Morris' data show similar success rates.[288]

The argument that most smokers and users of smokeless tobacco who quit do so without assistance relies on surveys of the small proportion of tobacco users who are able to quit each year. This population is not representative of the vast majority of current tobacco users, who have tremendous difficulty quitting. Furthermore, the fact that some smokers are able to quit without assistance does not reveal the difficulty experienced by these individuals or the extent to which they have previously relapsed. More than half of people presenting for treatment of alcohol or drug abuse who also smoke cigarettes report that quitting smoking would be harder than giving up their other drug of abuse.[289] Two-thirds of smokers who try to quit on their own relapse within 2 days, and approximately

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[288] Ryan FJ (Philip Morris Inc.), Cold turkey in Greenfield, Iowa: a follow-up study, in *Smoking Behavior: Motives and Incentives*, ed. Dunn WL (Washington DC: VH Winston & Sons, 1973), at 231-234. *See* AR (Vol. 8 Ref. 105).

[289] Kozlowski LT, Wilkinson A, Skinner W, *et al.*, Comparing tobacco cigarette dependence with other drug dependencies, *Journal of the American Medical Association* 1989;261:898-901. *See* AR (Vol. 41 Ref. 92).

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90% relapse within 3 months.[290] Sixty-eight percent of smokeless tobacco users who have attempted to quit have tried to do so an average of four times.[291]

The industry disputes FDA's analysis of 1991 and 1992 National Household Survey data, which reveal that 83% to 87% of moderate to heavy smokers feel addicted. The industry first argues that the question to smokers has no validity; FDA disagrees and notes that the industry cited the same survey result from the 1985 survey at another point in its comments. The industry then suggests that FDA's analysis of the 1991 and 1992 data is inconsistent with published reports. This is not true. The Substance Abuse and Mental Health Services Administration (SAMHSA) conducted two National Household Surveys, one in 1991 and another in 1992. The data referred to in the Proposed Rule were a calculation by the Centers for Disease Control and Prevention (CDC) of raw data obtained in the 1991 and 1992 surveys and presented at FDA's Drug Abuse Advisory Committee meeting in August 1994.[292] The CDC pooled the raw data from both surveys, weighted them accordingly, and then evaluated the data using parameters different from those outlined in the main findings of each survey. The CDC used the data to look at different age groups of users and different numbers of cigarettes smoked per day than did SAMHSA. Even if the calculations performed by SAMHSA had been used, the data

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[290] Hughes JR, Gulliver SB, Fenwick JW, *et al.*, Smoking cessation among self-quitters. *Health Psychology* 1992;11:331-334. *See* AR (Vol. 348 Ref. 5512).

[291] Severson HH, Enough snuff: ST cessation from the behavioral, clinical, and public health perspectives, *in Smokeless Tobacco or Health, an International Perspective*, Smoking and Tobacco Control Monograph 2, NIH Publication No. 93-3461 (Washington DC: GPO, 1993), at 281-282. *See* AR (Vol. 18 Ref. 5-1).

[292] Giovino GA, Zhu BP, Tomar S, *et al.*, *Epidemiology of Tobacco Use and Symptoms of Nicotine Addiction in the United States: A Compilation of Data from Large National Surveys*, presentation of the Centers for Disease Control and Prevention to the FDA's Drug Abuse Advisory Committee (Aug. 2, 1994). *See* AR (Vol. 459 Ref. 7820).

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would still show that, among those who smoke about a pack or more of cigarettes per day, 81% report feeling dependent.[293]

The tobacco industry also argues that FDA mischaracterized a 1993 report from the CDC that FDA cited in the Jurisdictional Analysis for the statement that more than 15 million Americans "tried to quit" each year and about 3% ultimately succeeded.[294] The industry contends that the survey did not ask specifically whether smokers had tried to quit, but whether smokers did not smoke at least 1 day during the preceding year. The industry concludes that this report is not relevant to whether smokers try to quit.

FDA disagrees. For daily smokers, the CDC counted one day of abstinence only if the smokers stated "they *quit* for at least 1 day."[295] The CDC logically interpreted these results as showing that 17 million daily smokers who reported not smoking for at least 1 day made an attempt to quit. According to the report, "the findings from this survey indicate that, in 1990 and 1991, approximately 42% of daily smokers abstained from smoking cigarettes for at least 1 day but that approximately 86% of these persons subsequently resumed smoking. The high rate of relapse is likely because of the addictive nature of nicotine."[296] FDA accepts CDC's interpretation of its survey.

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[293] Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Studies, *National Household Survey on Drug Abuse: Main Findings, 1991*, DHHS Publication Number (SMA)93-1980 (Rockville MD: DHHS, Public Health Service, 1993), at 127. *See* AR (Vol. 535 Ref. 96, vol. IILM).

[294] Centers for Disease Control and Prevention, Smoking cessation during previous year among adults—United States, 1990 and 1991, *Morbidity and Mortality Weekly Report* 1993;42(26):504-507. *See* AR (Vol. 66 Ref. 2).

[295] *Id.* at 504.

[296] *Id.* at 504-507.

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FDA also notes that CDC's estimate is consistent with other published estimates[297] and the tobacco industry's own tabulations of long-term quit rates. For example, a tobacco company has estimated that fewer than 4% of smokers who attempt to quit are able to quit permanently. *See* Jurisdictional Analysis, 60 FR 41668–41669.

FDA disagrees that survey results significantly distort the numbers of smokers who want to and have tried to quit. This method of data collection is a scientifically recognized and accepted mode of inquiry for prevalence studies, which is relied upon to determine the population prevalence of other disorders, including alcohol dependence, cocaine dependence, and depression.[298] Some of these are disorders for which, compared to tobacco use, interview methods would be less likely to reveal accurate results because of the criminal consequences associated with illicit drug use. Moreover, the authors of a study on this subject cited by the tobacco industry merely speculate that *some* smokers who say they want to quit *may* be dissembling, primarily on the basis of evidence that some smokers who claim to have quit smoking have been shown to be still smoking. At no time do these authors suggest that most smokers do not want to quit.[299]

4. The tobacco industry disputes that tobacco consumers continue to use despite knowledge of physical problems attributable to tobacco. The industry notes that, in one survey, a majority of smokers rated their overall health as good or excellent and

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[297] *See*, e.g., Hughes JR, Gulliver SB, Fenwick JW, *et al.*, Smoking cessation among self-quitters. *Health Psychology* 1992;11:331-334. *See* AR (Vol. 348 Ref. 5512).

[298] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 175-272. *See* AR (Vol. 535 Ref. 96, vol. III.B).

[299] Kozlowski LT, Herman CP, Frecker RC, What researchers make of what cigarette smokers say: filtering smokers' hot air. *Lancet* 1980;1(8170):699-700. *See* AR (Vol. 535 Ref. 96, vol. III.I).

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concludes from this that the smokers were not suffering ill health from tobacco use. The industry also criticizes studies cited by FDA that document high rates of smoking after catastrophic illness on the basis that (1) the sample sizes were small; and (2) some fraction of the subjects in the studies were able to quit.

After reviewing the evidence in the administrative record, FDA disagrees with the industry's position. To argue that a majority of smokers generally believe themselves in "good" or "excellent" health, the industry cites a Gallup poll originally cited by FDA.[300] In fact, contrary to the industry's argument, this Gallup poll demonstrates that smokers continue to use tobacco despite health problems. Sixty-five percent of smokers in the survey admitted that "smoking has already affected their health." Moreover, the data reveal that: (1) *significantly fewer* smokers than nonsmokers rated their health as "excellent"; and (2) smokers rated their overall condition as *significantly less healthy* than nonsmokers did. Thus, this survey supports FDA's contention that smokers persist in using tobacco despite knowledge that their health has been harmed by smoking.

The industry's criticism of data cited by FDA on smokers continuing to use tobacco after myocardial infarction, lung cancer, and laryngeal cancer is not persuasive. The industry offers no contradicting evidence, nor does it suggest any reason why the studies cited by FDA might not be generalizable to the larger population. In the absence of such reasons, FDA believes that the sample sizes were adequate to permit such generalization.

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[300] Gallup GH, *Smoking Prevalence, Beliefs, and Activities by Gender and Other Demographic Indicators* (Princeton NJ: Gallup Organization, 1993), at 20, 37. *See* AR (Vol. 86 Ref. 1165).

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The industry finally makes the argument that some people with devastating disease from tobacco are able to quit smoking. This contention misses the point. Even in the most drastic of circumstances, when patients have lost part of their body to cancer from smoking or had part of their heart muscle die from smoking, many still cannot stop. That any significant number of people return to smoking after such devastating tobacco-related disease is a powerful illustration of the addictiveness of nicotine.

h. Comments on Nicotine's Other Significant Pharmacological Effects

1. The tobacco industry argues that many substances and activities tangentially affect the brain, but that a reliable criterion for a "substantial" pharmacological effect is intoxication. According to the comment, nicotine does not produce intoxication, and therefore its pharmacological effects are not substantial.

FDA disagrees. FDA has presented dozens of scientific studies and reviews to show that nicotine has numerous substantial pharmacological effects on the human body. The most significant of these is addiction, discussed at length in section II.A.3., above. Other examples of substantial effects include significant molecular changes in the brain, effects on weight regulation, and substantial alterations of mood, alertness, and cognition, none of which the industry contests. The vast majority of drugs that FDA already regulates, whose pharmacological effects are indisputable, do not produce intoxication. FDA notes that nicotine can cause intoxication. Indeed, first-time users often become intoxicated.[301] Regular users do so rarely because they have developed an extremely high level of tolerance to this effect of nicotine.[302]

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[301] Surgeon General's Report, 1988, at 594. *See* AR (Vol. 129 Ref. 1592).

[302] *Id.* at 593-596.

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i. Comments on Whether Cigarettes and Smokeless Tobacco Deliver Pharmacologically Active Doses of Nicotine

1. Several professional organizations with expertise in pharmacology and addiction comment on the ability of cigarettes and smokeless tobacco to provide addictive doses of nicotine. These comments uniformly agree with the conclusion that cigarettes and smokeless tobacco do provide pharmacologically active doses of nicotine capable of producing addiction. These organizations include the College on Problems of Drug Dependence, which states:

> Nicotine is appropriately categorized as an addictive drug. Data from both animals and humans indicate that nicotine produces tolerance, physical dependence, reinforcing psychoactive effects and it thus has the potential for becoming an abused substance. Regular cigarette smokers and habitual smokeless tobacco users obtain sufficient quantities of nicotine to produce these effects .... *Cigarettes and smokeless tobacco serve as highly effective and efficient drug delivery devices. They provide nicotine in quantities and patterns that enable users readily to develop and sustain dependence.*[303]

The American Society of Addiction Medicine concludes that "*nicotine in cigarettes and in smokeless tobacco is a pharmacologically active agent that causes addiction in a high proportion of users.*"[304]

Similar conclusions were reached by the American Psychological Association, which observes that "*[c]igarettes and smokeless tobacco serve as highly effective and*

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[303] College on Problems of Drug Dependence, Comment (Nov. 6, 1995), at 1 (emphasis added). *See* AR (Vol. 700 Ref. 1021).

[304] American Society of Addiction Medicine, Comment (Dec. 29, 1995), at 1 (emphasis added). *See* AR (Vol. 528 Ref. 97).

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efficient drug delivery systems, which by their very design enable people to readily develop and sustain nicotine addiction."[305]

FDA agrees with these independent scientific bodies.

2. The tobacco industry takes issue with FDA's citations of studies to show that certain levels of nicotine cause pharmacological effects.

The tobacco industry argues that three studies cited by FDA to estimate the minimum pharmacological dose of nicotine do not show that tobacco products cause significant pharmacological effects. The industry also contends that two studies cited by FDA to show that smokers can control their nicotine intake do not reflect common tobacco consumption behavior.

The industry mischaracterizes FDA's reasons for citing the studies. FDA did not cite animal research and a study on the nicotine nasal spray to prove that cigarettes cause pharmacological effects in humans. Rather, the studies were cited to demonstrate that a very low blood level of nicotine that is easily attainable with cigarettes produces pharmacological effects across species. This observation complements overwhelming evidence from clinical, epidemiological, and laboratory studies showing that cigarettes and smokeless tobacco cause significant pharmacological effects in humans.

Similarly, FDA did not cite studies on the extremes of nicotine intake to demonstrate exactly how much nicotine every smoker obtains. Rather, the studies were cited to demonstrate that nicotine intake from cigarettes has the potential to vary widely across a range of levels that produce significant pharmacological effects in humans.

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[305] American Psychological Association, Comment (Dec. 28, 1995), at 2 (emphasis added). *See* AR (Vol. 531 Ref. 123).

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FDA also notes that the industry offers no data contradicting FDA's studies. The

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Nicotine's capacity to produce and sustain addiction, as described in section II.A.2., above, is another example of a significant pharmacological effect.

Because the vast majority of chronic smokers are highly tolerant to nicotine, not all of the pharmacological effects of nicotine are evident with every cigarette and pinch of smokeless tobacco. As described in section II.A.3.c.i., above, the severe degree of tolerance produced by nicotine seems to greatly exceed that produced by cocaine and to be more comparable to that produced by morphine in the reduction of responsiveness to acute doses after a period of repeated exposure.

4. The tobacco industry argues that there is no "addictive level" of nicotine. This contention is partly based on the claim that nicotine intake is not well correlated with quitting success. The industry also argues that FDA's Drug Abuse Advisory Committee did not identify a threshold addictive dose of nicotine. Without such an "addictive level," the industry concludes, the nicotine in tobacco products cannot have a substantial pharmacological effect.

FDA disagrees. The tobacco industry misinterprets the scientific literature on cessation studies, the actual conclusion reached by the Committee, and the concept of "addictive level."

A large body of literature has shown that nicotine dependence level is among the strongest general predictors of withdrawal severity and duration of abstinence. *See* section II.A.7.f., above.[310] These data support the conclusion that the relationship between level of drug intake and dependence level is similar to that observed with other

[310] Surgeon General's Report, 1988, at 315-321, 522-523. *See* AR (Vol. 129 Ref. 1592).

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forms of drug addiction, namely that level of drug intake is generally but not precisely correlated positively with dependence level and that there is wide individual variability.[311] It is because drug intake alone is not a perfect measure of dependence that diagnostic instruments such as the DSM are necessary for clinical practice.

The industry also misrepresents the findings of the FDA Committee, which concluded that all currently marketed cigarettes contain an addictive dose of nicotine, but that the data were not sufficient to determine a threshold dose below which the product would *not* pose a risk of addiction.[312] The main concern of the Committee was that, in attempting to set a lower limit, any error on the high side would permit the industry to market products that would be addictive to some persons. The Committee was particularly concerned that persons who have not developed tolerance to nicotine, such as children, might find even the doses posed by Benowitz and Henningfield (approximately one-tenth of the delivery of a typical cigarette) to be addictive.[313]

FDA concurs with the Committee that all currently marketed cigarettes contain addictive levels of nicotine.

5. The tobacco industry argues that any compensation occurring in response to cigarettes with lower yields of tar and nicotine is limited and of short duration. Thus, according to the industry, smokers of low-yield cigarettes do not obtain pharmacologically active doses of nicotine. The industry contends that this proposition is supported by an

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[311] *Id.* at 315-321.

[312] Transcript to the FDA Drug Abuse Advisory Committee, Meeting 27, "Issues Concerning Nicotine-Containing Cigarettes and Other Tobacco Products" (Aug. 2, 1994), at 346-353. *See* AR (Vol. 255 Ref. 3445).

[313] *Id.* at 346-353.

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article by Benowitz and Henningfield.[314] The industry also argues that smokers actually compensate for changes in tar delivery rather than nicotine delivery. Furthermore, it denies that cigarette vent-hole blocking is a significant means of compensation. The industry thus argues that compensation for nicotine does not occur.

FDA disagrees. Tobacco industry research demonstrates that smokers significantly compensate for nicotine. For example, research presented at a tobacco industry conference in 1974 demonstrated that, "whatever the characteristics of cigarettes as determined by smoking machines, the smoker adjusts his pattern to deliver his own nicotine requirements." *See* Jurisdictional Analysis, 60 FR 41663. Other examples of the tobacco industry's understanding of compensation are documented in the Jurisdictional Analysis. *See* 60 FR 41572–41575.

Furthermore, FDA cited research in the Jurisdictional Analysis demonstrating that the actual amount of nicotine delivered to the smoker does not correlate with the machine-measured yield of the cigarette and that smokers who smoke "low-yield" cigarettes have been shown to obtain substantially more nicotine than the advertised yield. *See* 60 FR 41659-41665. In one study, for example, the advertised yield of tested cigarettes ranged from 0.1 to 1.6 mg of nicotine, but the actual nicotine intake by the smokers asked to smoke these cigarettes ranged from 0.75 to 1.25 mg.[315] Other studies have also found that the nicotine levels measured in smokers' blood bear either no relationship or a minimal

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[314] Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. *New England Journal of Medicine* 1994;331:123-125. *See* AR (Vol. 28 Ref. 218).

[315] Gori GB, Lynch CJ. Analytical cigarette yields as predictors of smoke bioavailability. *Regulatory Toxicology and Pharmacology* 1985;5:314-326. *See* AR (Vol. 12 Ref. 142).

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relationship to the nicotine yield of the cigarettes being smoked and that machine-measured yields of low-tar/low-nicotine cigarettes significantly underestimate true rates of nicotine absorption. In most of these studies, the subjects were people who were smoking their usual brand of cigarettes and showed levels of nicotine not related to Federal Trade Commission (FTC) yields, thus refuting the suggestion that compensation is short-lived.[316]

The tobacco industry misrepresents the position of Benowitz and Henningfield on compensation. These authors have repeatedly published research demonstrating that smokers compensate with current cigarettes by smoking harder or by blocking the vent holes.[317]

In the Benowitz and Henningfield paper cited by the tobacco industry, the authors were discussing cigarettes—not currently on the market—with so little available nicotine that it would be impossible to compensate for reduced nicotine except by smoking an impractical number of cigarettes. The total nicotine content of these cigarettes would have been only about 5% of the content of currently marketed cigarettes and would have permitted a maximum delivery of only about 10% that of current cigarettes. The authors predicted that few smokers would permanently smoke the 200 or more cigarettes needed to obtain the nicotine intake typically delivered by 20 conventional cigarettes. Thus, Benowitz and Henningfield believed that, if denied access to regular nicotine cigarettes, smokers would either quit or adjust over time to substantially reduced nicotine intake.

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[316] Surgeon General's Report, 1988, at 158-159. *See* AR (Vol. 129 Ref. 1592).

[317] *Id.* at 158-163.

Henningfield JE, Kozlowski LT, Benowitz NL. A proposal to develop meaningful labeling for cigarettes. *Journal of the American Medical Association* 1994;272:312-314. *See* AR (Vol. 313 Ref. 4846).

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This prediction is entirely inapplicable to currently marketed "low-yield" cigarettes delivering 0.1 mg of nicotine as measured by the smoking machine; a smoker need smoke only about 30 of these to obtain the amount of nicotine obtained with 20 "full flavor" cigarettes.[318]

The tobacco industry's denial that vent blocking occurs misses important points of FDA's position on this issue. FDA has simply posed vent blocking as the most likely explanation for the well-documented fact that there is almost no difference in the nicotine levels observed in the bodies of smokers who smoke brands with widely varying FTC yields. Smoking more cigarettes is only one means by which smokers compensate. Vent blocking is another means at the smoker's disposal to compensate. Indeed, the studies relied on by the tobacco industry suggest that the frequency of vent blocking is inversely proportional to the yield of the cigarette. In other words, the lower the tar and nicotine yield of the cigarette, the more the smoker blocks the vent holes. These data support the position that vent blocking plays an important role in compensation. There are, in addition, other compensation mechanisms, such as smoking more of the cigarette than is smoked in testing machines, smoking more aggressively, and taking deeper inhalations.[319]

The tobacco industry contends that smokers may compensate for tar rather than for nicotine. This contention is contradicted by a very extensive body of literature, documented in detail in the 1988 Surgeon General's Report,[320] showing that, when the

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[318] Transcript to the FDA Drug Abuse Advisory Committee, Meeting 27, "Issues Concerning Nicotine-Containing Cigarettes and Other Tobacco Products" (Aug. 2, 1994), at 106. *See* AR (Vol. 255 Ref. 3445).

[319] Surgeon General's Report, 1988, at 153-158. *See* AR (Vol. 129 Ref. 1592).

[320] *Id.* at 153-169, 282-283.

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level of nicotine in cigarettes is manipulated, smokers alter their smoke intake. Although the relationship is not perfect, it is similar to that which has been observed with other addictive drugs in numerous animal studies and some human studies. That is, when the dose of the drug in the cigarette is increased, the number of unit doses that are self-administered decreases generally, although not proportionally. This results in the frequent observation of increased overall drug intake.[321]

Conversely, when the dose is decreased, the number of unit doses that are self-administered generally increases, although usually not proportionally. The relationship has been demonstrated with respect to cigarette smoking by: (1) administering nicotine to smokers via other routes, which results in decreased smoking; and (2) administering the nicotine blocker mecamylamine to smokers (which reduces the effects of nicotine on receptors in the brain), resulting in increased smoking.[322] A study on compensation for smokeless tobacco cited by the smokeless tobacco industry showed that users increased their consumption when switched to a low-nicotine product.[323]

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[321] *Id.* at 282-283.

[322] *Id.* at 165-169.

[323] Andersson G, Axell T, Curvall M, Reduction in nicotine intake and oral mucosal changes among users of Swedish oral moist snuff after switching to a low-nicotine product, *Journal of Oral Pathology & Medicine* 1995;24:244-250. *See* AR (Vol. 526 Ref. 95, vol. VII).

The low-nicotine product had a lower pH than the higher-nicotine product. Because lower pH reduces absorption *see* section II.D., below, measurements of nicotine intake cited by the industry do not accurately reflect compensation in this study.

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B. CONSUMERS USE CIGARETTES AND SMOKELESS TOBACCO TO OBTAIN THE PHARMACOLOGICAL EFFECTS OF NICOTINE AND TO SATISFY THEIR ADDICTION

In section II.A., above, the Agency concludes that the foreseeable pharmacological uses of cigarettes and smokeless tobacco establish that tobacco manufacturers intend their products to affect the structure and function of the body. The Agency may find additional evidence of such intent through evidence that consumers commonly use tobacco products for pharmacological effects. Where consumers use a product predominantly or nearly exclusively to obtain any of the effects on the structure or function of the body produced by a substance, such evidence would alone be sufficient to establish manufacturer intent. *See ASH v. Harris*, 655 F.2d 239-240.

The Agency made extensive findings regarding consumer use of tobacco products in the Jurisdictional Analysis. *See* 60 FR 41576-41581. FDA received comments from the tobacco industry, public health and medical organizations and practitioners, and other members of the public. Upon review of the evidence in the administrative record and careful analysis of the comments on the Jurisdictional Analysis, the Agency concludes that the evidence demonstrates that consumer use of cigarettes and smokeless tobacco for the pharmacological effects of nicotine is predominant, in fact nearly exclusive. Moreover, the Agency finds that other factors associated with tobacco use—including taste and habit—are significant to almost all consumers only by their association with nicotine's pharmacological effects on the brain. Thus, FDA finds that actual consumer use of cigarettes and smokeless tobacco for the pharmacological effects of nicotine provides an

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independent basis for the conclusion that these products are intended to affect the structure and function of the human body.[324]

In section II.B.1., below, FDA discusses its authority to consider evidence of consumer use in establishing intended use. FDA presents its major findings and responds to significant comments in sections II.B.2. and 3., below. In section II.B.4., below, FDA responds to all other substantive comments.

1. "Intended Use" May Be Established on the Basis of Actual Consumer Use

The legislative history of the Act clearly states that consumer use can be probative of a product's intended use. For example, the House Report on the Medical Device Amendments of 1976 states that "*[t]he Secretary may consider . . . use of a product in determining whether or not it is a device.*" H.R. Rep. 853, 94th Cong., 2d Sess. 14 (1976) (emphasis added), *reprinted in* An Analytical Legislative History of the Medical Device Amendments of 1976, Appendix III (Daniel F. O'Keefe, Jr. & Robert A. Spiegel, eds. 1976). Similarly, the legislative history of the 1938 Act states expressly that "the *use* to which the product is to be put *will determine the category into which it will fall.*" S. Rep. No. 361, 74th Cong., 1st Sess. 4 (1935) (emphasis added), *reprinted in* 3 Legislative History 660, 663.

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[324] In this case, there is evidence not only of actual consumer use, but other evidence of manufacturer intent, including: (1) evidence that nicotine's addictive properties and other pharmacological effects are foreseeable to a reasonable tobacco manufacturer; and (2) evidence from the statements, research, and actions of manufacturers establishing that they intend their products to affect the structure or function of the bodies of tobacco users. *See* sections II.A., C., and D. Thus, although the evidence establishes that consumers use cigarettes and smokeless tobacco predominantly or nearly exclusively for the pharmacological effects of nicotine, this finding is not necessary to permit reliance on the evidence of actual consumer use. Relied on in conjunction with the other evidence of manufacturer intent, evidence of actual consumer use provides substantial additional support for the Agency's conclusion.

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Like the legislative history, FDA's regulations on adequate directions for the use of drugs and devices also demonstrate that actual consumer use can be a basis for establishing a product's intended use. 21 CFR 201.5 (drugs); 21 CFR 801.5 (devices). Section 201.5, which specifies the "adequate directions" that must be provided on drug labeling, provides examples of the "intended uses" of a drug that must be included in any adequate labeling. These intended uses include both: (1) "uses for which it is prescribed, recommended, or suggested in its oral, written, print, or graphic advertising;" and (2) "*uses for which the drug is commonly used.*" 21 CFR 201.5 (emphasis added). Section 801.5 contains parallel provisions for devices. Because adequate directions for use are required only for the intended uses of a product, these regulations make the "common use" of a product a basis for determining "intended use."

Courts have also recognized that actual consumer use can be a persuasive basis for determining intent—even in the absence of other evidence that the manufacturer intends to affect the structure or function of the body. In *ASH*, the court explicitly recognized that actual "consumer intent" by itself could be a basis for imputing intent to the manufacturer:

> Clearly, it is well established "that the 'intended use' of a product, within the meaning of the Act, is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source." *Whether evidence of consumer intent is a "relevant source" for these purposes depends upon whether such evidence is strong enough to justify an inference as to the vendors' intent.* This requires a substantial showing. . . . In cases such as the one at hand, consumers must use the product predominantly—and in fact nearly exclusively—with the appropriate intent before the requisite statutory intent can be inferred.

655 F.2d at 239-240 (emphasis added). Similarly, in *NNFA v. Weinberger*, the court held that evidence before the Commissioner that vitamins "were used almost exclusively for

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therapeutic purposes" could be a proper basis to determine that the manufacturer intended a pharmacological use. 512 F.2d at 703.

When a finding of an intent to affect the structure and function of the body is based exclusively on evidence of actual consumer use, the evidence must meet a high threshold. As quoted above, the courts in *ASH* and *NNFA* have indicated that the evidence should show that the actual consumer use for drug purposes is "predominant" or "nearly exclusive." FDA's regulations contemplate that the use be shown to be at least "common." 21 CFR 201.5.

There is no requirement, however, that a product be used nearly exclusively as a drug before FDA may regulate it as a drug. To the contrary, a product that has both pharmacological uses and nonpharmacological uses can be regulated as a drug. *See United States v. Guardian Chemical Corp.*, 410 F.2d 157, 162-163 (2d Cir. 1969)(a solvent used both to dissolve kidney stones (a drug use) and to clean instruments (a nondrug use) was properly regulated as a drug). Consistent with this principle, the courts recognize that where, as here, there is other evidence of manufacturer intent, consumer use for drug purposes may be relevent evidence of intended use even if that use is not predominant or nearly exclusive. *See, e.g., United States v. An Article of Device . . . Tofness Radiation Detector*, 731 F.2d 1253, 1257 (7th Cir. 1984); *United States v. 789 Cases . . . Latex Surgeons' Gloves*, 799 F. Supp. 1275, 1285, 1294-95 (D.P.R. 1992); *United States v. 22 . . . devices . . . "The Ster-o-lizer MD-200."* 714 F. Supp. at 1165; *United States v. An Article of Device . . . "Cameron Spitler Amblo-Synonizer,"* 261 F. Supp. 243, 245 (D. Neb. 1966).

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Consistent with these authorities, the Agency finds that actual consumer use can be a basis for establishing the manufacturer's intended use for the product. Where the only evidence of intended use is the actual consumer use of the product, the Agency may need to show that the use of the product for pharmacological purposes is "predominant" or "nearly exclusive" before establishing that a product is intended to affect the structure or any function of the body. At a minimum, as set forth in FDA's regulations, the Agency should show that the use is "common" before relying exclusively on evidence of consumer use to establish intended use. Where, however, actual consumer use is only one of several types of evidence relied upon by the Agency, more limited evidence of consumer use can be used to support a finding that a product is "intended to affect the structure or any function of the body."

In the case of cigarettes and smokeless tobacco, as discussed below, the evidence establishes that the standard of "predominant" or "nearly exclusive" consumer use is met even though other types of evidence exist. Thus, the evidence of actual consumer use of cigarettes and smokeless tobacco provides an independent basis for establishing these products' intended pharmacological uses.

2. Consumers Use Cigarettes and Smokeless Tobacco for the Pharmacological Effects of Nicotine

The evidence on consumer use of cigarettes and smokeless tobacco convincingly demonstrates the intended use of such products for pharmacological purposes. In the following sections, FDA explains this conclusion and the epidemiological and experimental data that confirm that consumers *do* use cigarettes and smokeless tobacco predominantly for one or more of the pharmacological effects of nicotine.

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a. Epidemiological Evidence Shows That Consumers Use Cigarettes and Smokeless Tobacco for Pharmacological Effects

Epidemiological studies establish that the vast majority of consumers use tobacco for at least one of three pharmacological purposes: to satisfy a nicotine addiction; to receive the accompanying psychoactive effects, such as relaxation and stimulation; or to control weight.

To satisfy nicotine addiction. *If a tobacco consumer is addicted to nicotine, then* the key reason for use of the tobacco product is a pharmacological effect: the satisfaction of the addiction.

Based upon internationally accepted definitions of addiction from the American Psychiatric Association and the World Health Organization (WHO), major recent studies show that 77% to 92% of smokers are addicted to cigarettes. In various studies, smokers who met the criteria for addiction included those identified by self-report (90% addicted),[325] those who used tobacco six or more times (87% addicted),[326] those who were daily users for at least one month (77% to 92% addicted),[327] and those who reported any current use of cigarettes (80% addicted).[328] Studies show a *higher* percentage of

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[325] Hughes JR, Gust SW, Pechacek TF, Prevalence of tobacco dependence and withdrawal, *American Journal of Psychiatry* 1987;144(2):205-208. *See* AR (Vol. 81 Ref. 292).

[326] Woody GE, Cottler LB, Cacciola J, Severity of dependence: data from the DSM-IV field trials, *Addiction* 1993;88:1573-1579. *See* AR (Vol. 13 Ref. 150).

[327] Cottler L, Comparing DSM-III-R and ICD-10 substance use disorders, *Addiction* 1993;88:689-696. *See* AR (Vol. 13 Ref. 149).

[328] Hale KL, Hughes JR, Oliveto AH, Helzar JE, Higgins ST, Bickel WK, Cottler LB, Nicotine dependence in a population-based sample, in *Problems of Drug Dependence, 1992*, NIDA Research Monograph 132 (Washington DC: Government Printing Office, 1993). *See* AR (Vol. 39 Ref. 60).

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addiction among tobacco users than among users of other addictive drugs, including cocaine and heroin.[329]

Although there have been no population-based studies using DSM or WHO criteria to assess rates of addiction to smokeless tobacco, substantial evidence demonstrates that a high proportion of smokeless tobacco users meet individual criteria for addiction. *See* section II.A.3.c.ii., above. This evidence strongly supports the conclusion that a substantial proportion of such users are addicted.[330] In 1992, the Inspector General of the U.S. Department of Health and Human Services estimated that approximately 75% of young regular users of smokeless tobacco are addicted.[331]

Evidence also demonstrates that many tobacco users continue to consume tobacco for an additional pharmacological reason related to addiction: to avoid withdrawal symptoms.[332] As addiction specialist Jerome Jaffe has noted, "[w]ithdrawal from nicotine . . . regularly motivates continued smoking."[333]

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[329] Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology* 1994;2:244-268. *See* AR (Vol. 37 Ref. 4).

[330] Benowitz NL. Pharmacology of smokeless tobacco use: nicotine addiction and nicotine-related health consequence. in *Smokeless Tobacco or Health*, Smoking and Tobacco Control Monograph 2 (Washington DC: Government Printing Office, 1993), at 224. *See* AR (Vol. 93 Ref. 606).

[331] Department of Health and Human Services, Office on Smoking and Health, *Spit Tobacco and Youth* (Washington DC: Government Printing Office, 1992), at 8. *See* AR (Vol. 7 Ref. 76).

[332] Hughes JR, Higgins ST, Hatsukami D. Effects of abstinence from tobacco: a critical review. *Research Advances in Alcohol and Drug Problems* 1990;10:317-398, at 381. *See* AR (Vol. 535 Ref. 96, vol. III.G).

[333] Jaffe JH. Drug addiction and drug abuse. in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-573), at 529. *See* AR (Vol. 535 Ref. 96, vol. III.G).

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II.B.2.

For stimulation, sedation, mood alteration, and cognition. Studies also reveal that a large proportion of consumers use tobacco for other psychoactive effects. For example, a recent survey of young people 10 to 22 years old found that 72.8% of daily smokers and 53.8% of daily consumers of smokeless tobacco said they used tobacco for relaxation.[334] The 1988 Surgeon General's Report reviewed the epidemiological literature on the effects of smoking on mood: "The conclusion from this literature is that in the general population, persons perceive that smoking has functions that are relevant for mood regulation. Persons report that they smoke more in situations involving negative mood, and they perceive that smoking helps them to feel better in such situations."[335] The Surgeon General's Report also noted that "some cigarette smokers believe that smoking helps them to think and concentrate."[336] This is the belief of several prominent tobacco industry researchers.[337] Data demonstrating significant consumer use for the pharmacologically mediated effects of nicotine on mood and arousal are summarized in the Jurisdictional Analysis. *See* 60 FR 41579–41580.

To control weight. Numerous studies show that tobacco use by many people is at least partially motivated by their belief that tobacco will help them control their weight.

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[334] Centers for Disease Control and Prevention, Reasons for tobacco use and symptoms of nicotine withdrawal among adolescents and young adult tobacco users—United States, 1993. *Morbidity and Mortality Weekly Report* 1994;43(41):745-750. *See* AR (Vol. 43 Ref. 162).

[335] Surgeon General's Report, 1988, at 399. *See* AR (Vol. 129 Ref. 1592).

[336] *Id.* at 382.

[337] Robinson J. Transcript to the FDA Drug Abuse Advisory Committee, Meeting 27, "Issues Concerning Nicotine-Containing Cigarettes and Other Tobacco Products" (Aug. 2, 1994), at 227. *See* AR (Vol. 255 Ref. 3445).

Warburton DM, Nicotine: an addictive substance or a therapeutic agent, *Progress in Drug Research* 1989;33:9-41, at 25. *See* AR (Vol. 140 Ref. 1657).

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For example, in two surveys of young people, between one-third and one-half of smokers said that weight control was a reason for their smoking.[338] Additional data on the use of tobacco products for weight control are summarized in the Jurisdictional Analysis. *See* 60 FR 41580–41581.

b. Experimental Evidence Shows That Consumers Use Cigarettes and Smokeless Tobacco Products for Pharmacological Effects

As described in section II.A.3.c.i., above, overwhelming laboratory data demonstrate that nicotine's pharmacological effects are central to tobacco use. Three findings from experimental studies particularly show that consumers smoke cigarettes and consume smokeless tobacco for the pharmacological effects of nicotine.

Nicotine reinforces tobacco consumption. Like other addictive substances such as amphetamine, morphine, and cocaine, nicotine acts on a key "reward" pathway in the brain—known as the mesolimbic system—to reinforce its own consumption.[339] As even the tobacco industry has noted, the "reward" generated by this pathway may explain why people eat food, drink water, and consume salt. The ability of nicotine to generate a similar "reward" for tobacco consumption reflects its pharmacological power and represents a clear reason why consumers use tobacco products. The data supporting nicotine's role in the "reward" system are discussed in section II.A.3.c.i., above.

Nicotine controls smoking behavior. It has been convincingly demonstrated that smokers adapt their cigarette consumption to maintain the pharmacological effect of nicotine in

[338] Surgeon General's Report, 1988, at 438-441. *See* AR (Vol. 129 Ref. 1592).

[339] *See, e.g.*, Corrigall WA, Franklin KBJ, Coen KM, *et al.*, The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. *Psychopharmacology 1992;107:285-289. See* AR (Vol. 8 Ref. 93-4).

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the brain. Thus, smokers given cigarettes lower in nicotine change their smoking behavior to obtain more nicotine, and those given cigarettes higher in nicotine than their usual brand modify their behavior to obtain less. When given a drug to reduce the effect of nicotine in the brain, smokers will consume more of the same cigarettes, even though nothing else has changed. This is compelling evidence that nicotine plays a pivotal role in why consumers use tobacco products. These data are discussed in detail in section II.A.5., above.

Nicotine in other forms affects tobacco consumers. The ability of nicotine nasal spray to produce some of the classic characteristics of addiction to nicotine supports the position that tobacco users seek tobacco primarily for the systemic pharmacological effects of nicotine. In contrast to cigarette smoke, aqueous nicotine spray does not provide any pleasing sensory characteristics. In fact, the spray can be irritating and unpleasant to use, and excessive use can cause nasal ulcerations. Notwithstanding the unpleasantness of the nicotine delivery mechanism and the presence of painful ulcerations that were further aggravated by continued use of the spray, some participants in clinical trials submitted to FDA used the spray to maintain nicotine dependence.[340]

Studies on nicotine replacement therapies also demonstrate efficacy in maintaining abstinence from smoking.[341] The ability of nicotine to promote abstinence, even when delivered through the skin, without any taste or flavor, demonstrates its key role in maintaining tobacco consumption.

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[340] FDA Drug Abuse Advisory Committee background information (Aug. 1, 1994), Joint Abuse Liability Review of Nicotine Nasal Spray. *See* AR (Vol. 9 Ref. 117).

[341] *See* appendix 1 to Jurisdictional Analysis at 62-82. *See* AR (Vol. 1 Appendix 1).

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c. The Data Do Not Support the Industry's Claim That Consumers Seek Nicotine for Its Sensory Effects Rather than Its Pharmacological Effects

The tobacco industry responds to the overwhelming evidence that nicotine's pharmacological actions are central reasons for tobacco consumption by arguing instead that nicotine's key role in tobacco products is for flavor. According to the industry, the nonpharmacological actions of nicotine such as "flavor" are so essential to consumers that the nicotine level in each cigarette and unit of smokeless tobacco must be carefully controlled.

This argument in no way contradicts any of the experimental and epidemiological evidence showing that consumers use tobacco products for the pharmacological effects of nicotine. These studies prove nicotine's central pharmacological importance by demonstrating, for example, that: (1) nicotine causes psychoactive effects characteristic of addiction even when delivered by nonoral routes, where there is no "flavor" at all; and (2) the vast majority of smokers are addicted to tobacco products.

Moreover, the industry's position that nicotine's primary role is to provide flavor is inconsistent with the evidence. First, the industry's position is flatly contradicted by numerous statements of its own scientists and executives. Several industry documents dismiss the role of nicotine in flavor. For example, in 1974, an American Tobacco Company manager concluded that Pall Mall and Lucky Strike cigarettes tasted virtually the same even after the addition of extraneous nicotine (referred to as "Compound W"); according to the manager, "increasing the level of nicotine in the smoke by the addition of

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Compound W has *little, if any,* effect on taste."[342] A Philip Morris presentation that discusses the importance of flavor in ultra-low cigarettes states flatly that "nicotine is an inexpensive, *tasteless* constituent."[343] Philip Morris' comments similarly contradict the industry's position that nicotine has a significant role in the flavor of cigarettes. These comments state that Philip Morris conducted extensive investigations into the flavors in cigarette smoke using an "olfactometer," yet Philip Morris claims that "[n]one of that olfactometer work involved nicotine at all," an unlikely omission if nicotine is an important flavor component.[344]

Tobacco industry documents also reveal that the industry draws a consistent distinction between nicotine's role in tobacco use and the role of flavor. A Brown & Williamson study emphasized the importance of nicotine delivery over all other product features and specifically distinguished the effects of nicotine from the taste and flavor characteristics of tobacco:

> In considering which product features are important in terms of consumer acceptance, the nicotine delivery is one of the more obvious candidates. *Others include the taste and flavour characteristics* of the smoke, physical features such as draw resistance and rate of burn, and the general uniformity of the product, to name but a few. The importance of nicotine hardly needs to be stressed, as it is so widely recognised.[345]

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[342] Memorandum from Irby RM (manager, new products division) to McCarthy JB (executive vice president, research and development), *Nicotine Content of Reconstituted Tobacco* (Jun. 5, 1974), at 3-4 (emphasis added). *See* AR (Vol. 26 Ref. 357-3)

[343] Philip Morris Inc., First Speaker, Merit Team Remarks (Jan. 14, 1976), at 3 (emphasis added). *See* AR (Vol. 640 Ref. 2).

[344] Philip Morris Inc., Comment (Apr. 19, 1996), at 47. *See* AR (Vol. 700 Ref. 226).

[345] BATCO, *Project Wheat-Part 1: Cluster profiles of U.K. male smokers and their general smoking habits*, Southampton, England (Jul. 10, 1975), at 3-4 (emphasis added). *See* AR (Vol. 20 Ref. 204-1).

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An internal RJR document shows that the industry views nicotine's role as pharmacological and distinct from the smoke components that provide flavor:

> If nicotine is the sine qua non of tobacco products, and tobacco products are recognized as being attractive dosage forms of nicotine, then it is logical to design our product - and where possible our advertising - *around nicotine delivery rather than tar delivery or flavor.*[346]

Other industry documents further demonstrate that the industry understands that nicotine's role is primarily pharmacological and that any sensory role is secondary. A variety of industry documents shows that industry knows that "satisfaction" comes from inhalation of nicotine into the lungs and absorption into the bloodstream. *See* Jurisdictional Analysis, 60 FR 41773–41774. Inhalation is necessary only to provide systemic pharmacological effects; it would be unnecessary if nicotine's role were to provide sensory effects. The statements of tobacco industry scientists confirm that nicotine's pharmacological effects are the primary reason for tobacco use. A leading tobacco research director noted as early as 1972 that "[t]he primary incentive to cigarette smoking is the immediate salutary effect of inhaled smoke upon body function . . . . *the physiological effect serves as the primary incentive; all other incentives are secondary.*"[347] As recently as 1992, RJR researchers recognized that "smokers use cigarettes primarily as a 'tool' or 'resource' that provides them with needed psychological benefits (increased mental alertness; anxiety reduction, coping with stress)."[348]

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[346] Teague CE. *Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of Nicotine Therein* (Feb. 2, 1973), at 3 (emphasis added). *See* AR (Vol. 531 Ref. 125).

[347] Dunn WL, Philip Morris Research Center. *Motives and Incentives in Cigarette Smoking* (1972), at 3-4 (emphasis added). *See* AR (Vol. 34 Ref. 582).

[348] Robinson JH, Pritchard WS. The role of nicotine in tobacco use. *Psychopharmacology* 1992; 108: 397-407 (emphasis added). *See* AR (Vol. 104 Ref. 945).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

Literally dozens of such statements—made over decades by tobacco researchers and executives from virtually every major company—expose the industry's knowledge that consumers use tobacco products primarily for pharmacological effects. These statements are analyzed in depth in section II.C.2., below. By contrast, over this long period, there are virtually no tobacco company studies supporting the importance of the purported "sensory effects" of nicotine.

Second, the industry offers no persuasive data that nicotine contributes significantly to desirable flavor. FDA has reviewed all seven studies cited by the tobacco industry to demonstrate a significant "sensory" role for nicotine and finds them unpersuasive.

The industry cites a single abstract, based on research partially funded by RJR, to justify the claim that nicotine provides "trigeminal ('throat grab') stimulation that is enjoyed by smokers." The abstract describes a single study of trigeminal nerve manipulation in rats.[349] It is impossible to conclude from this study that nicotine stimulates the human trigeminal nerve in any manner significant to smokers.[350]

The industry cites a single paper to show that nicotine provides aroma "that is enjoyed by smokers." This research is based on recordings of the olfactory nerve in frogs.

[349] Silver WL, Walker DB, *Nasal trigeminal chemoreception: response to nicotine*, presented at the Ninth Annual Meeting of the Association for Chemoreceptor Sciences, Sarasota FL (1987). *See* AR (Vol. 535 Ref. 96. vol. III.M).

[350] The industry's "trigeminal nerve" theory seems to be based in part on an anatomic misunderstanding. The industry proposes that the sensation of "throat grab" is caused by nicotine stimulation "in the back of the throat (where trigeminal nerve endings are located)." In fact, sensation to the back of the throat (pharynx) in humans is provided by the glossopharyngeal nerve, not by the trigeminal nerve. *See* Williams PL, Warwick R, eds., *Gray's Anatomy*, 37th ed. (Philadelphia: WB Saunders, 1989), at 1112. *See* AR (Vol. 711 Ref. 8).

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It is impossible to conclude from this study that nicotine creates an aroma of any significance to smokers.[351] Indeed, another study also cited by the industry concluded that reducing the olfactory stimulus of cigarettes had a minor effect on smoking behavior.[352]

RJR cites one article from 1952 and three recent studies to support the contention that the sensory aspects of nicotine consumption are more important to users than its pharmacological effects.

In a 1952 article cited by RJR for the proposition that nicotine plays an important role in the taste and flavor of cigarette smoke, there are no data on this subject.[353] The relevant statements are merely the authors' speculations. In fact, the authors speculated about the flavors of various types of tobacco leaves, not about the specific flavor of nicotine. Nor did the authors distinguish between flavor and pharmacological effects of nicotine; to the contrary, a portion of the article omitted by the comment states that "the smoker's desires are not satiated by" a low-nicotine leaf. This observation is consistent with the conclusion that consumers value nicotine for its pharmacological effects.

A more recent study cited by RJR attempted to quantify the sensory responses to cigarettes containing varying levels of nicotine.[354] This study did not even consider

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[351] Thuraut N, Reisner B, Kobal G. Responses recorded from the frog olfactory epithelium after stimulation with r(+) - and S(-) - nicotine, *Chemical Senses* 1995;20(3):337-344, at 342. *See* AR (Vol. 535 Ref. 96, vol. III.M).

[352] Baldinger B, Hasenfratz M, Battig K. Switching to ultralow nicotine cigarettes: effects of different tar yields and blocking of olfactory cues, *Pharmacology, Biochemistry and Behavior* 1995;50(2):233-239, at 238. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[353] Darkis FR, Baisden LA, Gross PM, Wolf FA. Flue-cured tobacco: chemical composition of rib and blade tissue, *Industrial and Engineering Chemistry* 1952;44(2):297-301, at 300-301. *See* AR (Vol. 519 Ref. 103, vol. II).

[354] Gordin HH, Perfetti TA, Mangan PP. A quantification of sensory responses related to dynamic cigarette performance variables, *Tobacco Science* 1987;31:23-27. *See* AR (Vol. 519 Ref. 103, vol. II).

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whether any sensory responses to nicotine are important to smokers. The authors did not mention the number of subjects in the study. Nor did they account for the fact that cigarettes with varying nicotine levels also were different in many other ways; for example, they had different tip drafts, tipping porosities, plug wraps, and air dilution. Much of the data were not published with the study. FDA notes that this study—despite serious flaws—still found that tobacco taste was *not* associated with nicotine content.

A second recent study cited by RJR attempted to determine the smallest amount of nicotine change detectable to the user.[355] It did not address whether any nicotine change produces any important sensory effects. The authors concluded only that there is a detectable "perceptual response" to nicotine, which could be described as either throat harshness or "strength." The study did not distinguish between sensory and central pharmacological effects of nicotine.

The third recent study is an RJR presentation at a conference held in 1994, after FDA's investigation into nicotine was under way.[356] The presentation purported to show that nicotine's sensory effects are important in a consumer's acceptance of tobacco products, but the study failed to support this claim. Indeed, a principal author of the study conceded to FDA in 1994 that "we were not able to separate out the importance of the

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[355] Gordin HH, Perfetti TA, Hawley RW, Nicotine just noticeable difference study of full flavor low "tar" and ultra low "tar" non-menthol 85mm products, *Tobacco Science* 1988;32:62-65. *See* AR (Vol. 519 Ref. 103, vol. II).

[356] Pritchard WS, Robinson JH, *The Sensory Role of Nicotine in Cigarette "Taste," Smoking Satisfaction and Desire to Smoke*, presented at the International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II, Montreal (Jul. 21-24, 1994). *See* AR (Vol. 519 Ref. 103, vol. II).

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sensory aspects versus the pharmacological."[357] FDA notes that this study, despite serious flaws, still found that nicotine levels had *no* effect on smooth taste, harsh taste, or aftertaste of cigarettes.

Thus, the industry has presented no data that show that nicotine's flavor or sensory effects are important to consumer acceptance. Even if the industry had produced evidence to support its position, however, nicotine's pharmacological effects would still explain virtually all consumer use. As described in section II.B.3., below, the sensory aspects of tobacco consumption are important to consumers only in how they are linked to the pharmacological effects of nicotine.

Compared with the hundreds of studies conducted around the world demonstrating the pharmacological significance of nicotine to tobacco consumers—a conclusion that reflects universal scientific agreement—the evidence to support the assertion that nicotine's sensory role is important to consumers is unconvincing. Thus, the industry has provided no basis to conclude that nicotine's role in tobacco use is to provide taste, flavor, or any other nonpharmacological sensation.

3. Other Factors Associated with Tobacco Use Are Secondary to Pharmacological Effects

FDA has established above that consumers use tobacco products for the pharmacological effects of nicotine. The tobacco industry argues that consumers use tobacco for a variety of nonpharmacological purposes, including for taste, out of habit and ritual, and for social reasons. The Agency recognizes that there are many effects of

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[357] Robinson J. Transcript to the FDA Drug Abuse Advisory Committee, Meeting 27, "Issues Concerning Nicotine-Containing Cigarettes and Other Tobacco Products" (Aug. 2, 1994), at 228. *See* AR (Vol. 255 Ref. 3445).

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tobacco use perceived by some consumers as nonpharmacological in nature. In surveys, for example, some tobacco users say they like the taste of the product; others report enjoying the ritual involved in its consumption. The evidence before the Agency demonstrates, however, that the nonpharmacological factors associated with tobacco consumption are secondary to the pharmacological reasons for consumer use of tobacco. Indeed, FDA concludes that consumers use tobacco products "nearly exclusively" for the pharmacological effects of nicotine.

This conclusion is supported by comments from the Coalition on Smoking OR Health, representing the American Heart Association, American Lung Association, and American Cancer Society. The Coalition explains:

> The physicians and health professionals who comprise our organizations provide the health care for virtually all tobacco users in the United States. Based upon our long term experience as well as our review of the scientific literature, it is our conclusion that the *vast majority of people who use nicotine containing cigarettes and smokeless tobacco products do so to satisfy their craving for the pharmacological effects of nicotine*; that is, to satisfy their drug dependence or addiction. While the published scientific literature on the point is conclusive in our scientific opinion, there may be no better evidence of the reason people use these products than the accumulative, daily experience of the health care professionals who are our members.[358]

One basis for FDA's finding of nearly exclusive tobacco use for nicotine's pharmacological effects is that tobacco products do not exist commercially without nicotine. If taste, for example, were an independent reason for use of tobacco products—as claimed by the industry—one would expect to find that very-low-nicotine products that

[358] Coalition on Smoking or Health, Comment (Jan. 2, 1996), at 6 (emphasis added). *See* AR (Vol. 533 Ref. 102).

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preserve tobacco taste would be popular on the market. But there are no such products. The tobacco industry itself knows that a tobacco product without nicotine is not acceptable to consumers. For example, an attorney representing RJR stated that the company would never eliminate nicotine from its cigarette alternative, because "without nicotine, you don't have a cigarette."[359] A former Philip Morris researcher similarly stated that it was well-known within Philip Morris that nicotine delivery was more important than flavor in consumer acceptance of cigarettes. According to this researcher, it was believed within the company that while consumers might accept a cigarette that had adequate nicotine but marginal flavor, they were unlikely to accept a cigarette with relatively good flavor but "not enough" nicotine.[360]

A second basis for FDA's finding is that the details of tobacco use can be distinguished from the basic motivation for tobacco use. For example, researchers have demonstrated that consumers will pick a favorite cigarette brand among several that deliver adequate nicotine.[361] Habits may also explain specific patterns of cigarette consumption. For example, a smoker may enjoy smoking during his afternoon work break; another may like to smoke in the company of a particular friend. These factors commonly determine the details of use of many addictive substances, including opioids

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[359] Memorandum of meeting between Hunt PB, representing RJR Nabisco Inc., and FDA representatives (Oct. 23, 1987). *See* AR (Vol. 34 Ref. 558).

[360] Declaration of Uydess IL (Feb. 29, 1996), at 11-14. Comments concerning this declaration are addressed in section II.C.6., below. *See* AR (Vol. 638 Ref. 1).

[361] Boren JJ, Sitzer ML, Henningfield JE, Preference among research cigarettes with varying nicotine yields, *Pharmacology, Biochemistry and Behavior* 1990;36(1):191-193. *See* AR (Vol. 535 Ref. 96, vol. III.A).

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and alcohol.[362] But they are separate from the underlying reason for such use, the pharmacological effects of the drugs.

Third, FDA agrees with experts in the field of addiction medicine that nonpharmacological factors associated with tobacco use are important to consumers only because they have become inextricably linked to nicotine's pharmacological effects. Extensive research in the field of behavioral psychology has demonstrated how animals and people come to associate environmental stimuli (taste, rituals, etc.) with the pharmacological effects of addictive drugs. In the extreme form, providing the stimulus alone leads to the user experiencing the pharmacological effect of the drug. This is called a "conditioned response." Thus, a heroin user who says he likes the feel of the needle in his arm has linked the sensation with the pharmacological "high" that inevitably follows. This heroin addict may even report a "high" after the injection of saline.[363] But he or she still injects "nearly exclusively" for the pharmacological effects of heroin.

Similarly, evidence in animals and humans demonstrates that nonpharmacological factors such as taste and habit are important to tobacco consumers only because they have become inextricably linked to the effects of the addictive drug. As one prominent addiction specialist noted, "Animal experiments support the view that the sensory and

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[362] Surgeon General's Report, 1988, at 15. *See* AR (Vol. 129 Ref. 1592).

[363] O'Brien CP, Testa T, Temes J, Greenstein R, Conditioning Effects of Narcotics in Humans, in *Behavioral Tolerance: Research and Treatment Implications*, NIDA Research Monograph 18 (Washington DC: Government Printing Office No. 017-024-00899-8, Jan. 1978), at 67-71. *See* AR (Vol. 535 Ref. 96, vol. III.L).

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olfactory stimuli associated with tobacco-using behavior function as conditioned stimuli due to their previous association with nicotine."[364]

Clinicians who treat patients dependent upon tobacco products have reached the same conclusion.[365] For example, some smokers identify the sensation of "tracheal scratch" associated with inhalation as pleasurable. But, as the American Society of Addiction Medicine (ASAM) comments:

> The tracheal 'scratch' which arises from the inhalation of cigarette smoke is a sensation which has become paired with the absorption of nicotine into the bloodstream and the consequent effects of nicotine on the brain. *People do not smoke for the 'scratch'; they smoke for the nicotine.* The "scratch" tells the smoker that nicotine is on its way to the brain and provides some indication of the relative dose which will shortly be coming.[366]

Other evidence of "conditioned responses" comes from studies of the early stages of tobacco withdrawal, when providing the environmental stimuli of smoking without nicotine (i.e., very-low-nicotine cigarettes) alleviates some of the abstinent smokers' discomfort.[367] This is analogous to heroin users feeling a psychological benefit from injecting saline when heroin is not available.[368] In both cases, the benefits of the

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[364] Jaffe JH, Tobacco smoking and nicotine dependence, in *Nicotine Psychopharmacology* (Oxford: Oxford University Press, 1990), 1-29, at 14. *See* AR (Vol. 535 Ref. 96, vol. III.G).

[365] Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[366] American Society of Addiction Medicine, Comment (Dec. 29, 1995), at 5 (emphasis added). *See* AR (Vol. 528 Ref. 97).

[367] Butschky MF, Bailey D, Hemmingfield JE, Pickworth WB, Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers, *Pharmacology, Biochemistry and Behavior* 1995;50(1):91-96. *See* AR (Vol. 442 Ref. 7484).

[368] O'Brien CP, Testa T, Tennet J, Greenstein R, Conditioning Effects of Narcotics in Humans, in *Behavioral Tolerance: Research and Treatment Implications*, NIDA Research Monograph 18 (Washington DC: Government Printing Office No. 017-024-00899-8, Jan. 1978), at 67-71. *See* AR (Vol. 535 Ref. 96, vol. III.L).

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nonpharmacological stimuli rapidly decrease as the stimuli are no longer associated with the drug's effects.[369]

ASAM concluded: "People who use tobacco products build up rituals around nicotine ingestion and experience sensations in the process of using tobacco that become valuable to them. However, *these rituals would not exist, and the sensations would be of no value, but for the associated delivery of nicotine to the brain.*"[370] Thus, when someone says he or she smokes for the "taste" or "feel" or "ritual" of cigarette consumption, these "reasons for use" are inextricably tied to the pharmacological effects of nicotine.[371]

Accordingly, FDA concludes that consumers use tobacco products "predominantly" and "nearly exclusively" for one or more of the pharmacological effects of nicotine.

4. Responses to Additional Comments

a. General Comments on Consumer Use

1. The American Society of Addiction Medicine (ASAM) argues that the common practice of inhaling cigarette smoke demonstrates that consumers use cigarettes for the pharmacological effects of nicotine. According to ASAM, because of the relatively

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[369] *Id.*

Butschky MF, Bailey D, Henningfield JE, Pickworth WB, Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers, *Pharmacology, Biochemistry and Behavior* 1995;50(1):91-96. *See* AR (Vol. 442 Ref. 7484).

[370] American Society of Addiction Medicine, Comment (Dec. 29, 1995), at 14 (emphasis added). *See* AR (Vol. 528 Ref. 97).

[371] Surgeon General's Report, 1988, at 58-59. *See* AR (Vol. 129 Ref. 1592).

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low pH of cigarette smoke, nicotine absorption occurs to a significant extent only in the lungs. Conversely, ASAM notes that no important sensory effects are known to result from cigarette smoke in the lungs. Thus, ASAM concludes that "inhalation is the key to nicotine absorption from cigarettes, and there is no reason other than nicotine absorption for the consumer to inhale the smoke."[372]

ASAM further notes that tobacco advertisements historically encouraged consumers to inhale cigarette smoke; according to ASAM, such evidence demonstrates industry intent to ensure adequate nicotine delivery to smokers and thereby achieve substantial pharmacological effects.

FDA agrees that inhalation demonstrates that consumers use cigarettes for substantial pharmacological effects. According to *Gray's Anatomy*, there are no taste or smell receptors below the level of the larynx.[373] No evidence suggests that smokers enjoy any physical sensations associated with smoke in their lungs other than by association with the pharmacological effects of nicotine. Yet smokers learn to inhale—despite such unpleasant reactions as coughing—when the only reason to do so is nicotine absorption

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in smoke, it must be presumed that this is its preferred method of absorption and *thus why people inhale smoke.*"[374]

2. The smokeless tobacco industry argues that FDA fails to distinguish among different smokeless tobacco products. The comment contends that FDA has based its conclusions entirely on evidence about moist snuff and that this evidence is inapplicable to chewing tobacco.

FDA disagrees that it has ignored the distinction between moist snuff and chewing tobacco or that its evidence applies only to moist snuff. As described in the Jurisdictional Analysis, Benowitz and colleagues found that the rate and amount of nicotine absorption was similar for oral snuff and chewing tobacco in ten healthy volunteers.[375] See Jurisdictional Analysis, 60 FR 41572. The total amount of nicotine absorbed from snuff and chewing tobacco was estimated to be 3.6 mg and 4.5 mg, respectively.[376] This study confirms that as much or more nicotine is absorbed from each of these products as from cigarettes.

Additionally, in a study submitted by the industry, Walsh and colleagues reported on the use of smokeless tobacco in 1,300 U.S. college athletes.[377] Of those surveyed who

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[374] Letter from Ayres CI (BATCO) to Kohnhorst EE (Brown & Williamson), transmitting partial summary of issues presented at Montebello Research Conference in 1982, at BW-W2-03949 (emphasis added). *See* AR (Vol. 34 Ref. 584-1).

[375] Benowitz NL, Porchet H, Sheiner L, *et al.*, Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum, *Clinical Pharmacology and Therapeutics* 1988;44:23-28. *See* AR (Vol. 12 Ref. 134-1).

[376] *Id.*

[377] Walsh MM, Hilton JF, Ernster VL, Masouredis CM, Grady DG. Prevalence, patterns, and correlates of spit tobacco use in a college athlete population. *Addictive Behavior* 1994;19:411-427. *See* AR (Vol. 526 Ref. 95, appendix VIII).

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used smokeless tobacco, 39% reported using snuff only, 41% reported using both snuff and chewing tobacco, and 16% reported using chewing tobacco only. (Four percent failed to indicate the type of smokeless tobacco used.) Athletes who used both snuff and chewing tobacco generally reported patterns of use that were similar to those of athletes who used snuff only. This study supports similar patterns of use in both snuff and chewing tobacco users and demonstrates use of either moist snuff or chewing tobacco for similar pharmacological effects, such as relieving stress, satisfying strong cravings, and relieving the discomfort of withdrawal.

Thus the use, effects, and nicotine absorption from chewing tobacco compare with moist snuff and cigarettes. *See also* section II.D., below.

b. Comments on Tobacco Use To Satisfy Addiction

1. The tobacco industry argues that FDA's claim in the Jurisdictional Analysis that 75% to 90% of smokers consume cigarettes to satisfy addiction is factually unsupported. The industry contends that FDA selectively extracted pieces of data from various studies to support this rate of nicotine dependence and that the studies FDA relied upon were conducted in sample populations of patients of substance abuse clinics who would have higher "scales of dependence" than the general population.

FDA disagrees. The Agency did not selectively choose studies or selectively extract data from the studies on which it relied to support the reported rates of nicotine dependence. Rather, FDA chose from the published literature those studies that met the following criteria: the study used a definition of addiction established internationally by major public health organizations, the study was capable of estimating the prevalence of nicotine addiction in a well-defined population, and the study used appropriate research

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methods, such as random sampling of a well-defined population, to estimate the prevalence of nicotine addiction. No study relied on surveying smokers at tobacco cessation clinics.

The four studies identified by FDA as satisfying the stated selection criteria for determining the population prevalence of nicotine addiction utilize two data sets and smoking populations. These sample populations represent a generalizable spectrum of smokers.

One of these populations (utilized in a study by Hughes *et al.*)[378] included otherwise healthy, non-drug-abusing patients representative of a well-defined population. This was not a selectively extracted population, nor did it have an elevated prevalence of nicotine addiction, as argued by the tobacco industry. It consisted of over 1,000 middle-aged smokers randomly sampled from a well-defined population of male heads of households, who were otherwise representative of men of that age. The men entered the study by identifying themselves as smokers. These men, on average about 51.1 years of age, were estimated to have a lifetime prevalence of nicotine addiction of 90%. The authors report that smoking habits of the men in this study were similar to those reported in previous studies of middle-aged men.

The tobacco industry contests these data on the grounds that: (1) the subjects are representative of the heaviest 22% of U.S. smokers; and (2) the authors at the time argued that the DSM criteria for nicotine addiction were too expansive. The industry's first point is based on a statistical misinterpretation. The industry argues that since the average

[378] Hughes JR, Gust SW, Pechacek TF. Prevalence of tobacco dependence and withdrawal. *American Journal of Psychiatry* 1987;144(2):205-208. *See* AR (Vol. 81 Ref. 292).

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cigarette consumption in the study was 28 cigarettes per day, and because 22% of smokers in 1991 consumed over 25 cigarettes per day, then the study applies to "at most 22 percent of smokers." But this reasoning confuses average and median consumption. The heaviest 22% of smokers, on average, consume far more than 25 or 28 cigarettes per day. For example, in 1985, almost half of the smokers in the group who smoked more than 21 cigarettes per day reported smoking 40 or more cigarettes a day.[379] Thus, the average number of cigarettes smoked by heavy smokers is well above 28 per day. Accordingly, the smokers represented in the Hughes study smoke less, on average, than "the heaviest" smokers identified by the comment.

The industry's second argument concerning the authors' view of the DSM criteria is irrelevant. Although the researchers were initially surprised at the high rates of dependence revealed in this study, the DSM criteria have retained credibility and are widely accepted by clinicians for diagnosing substance dependence.

The second sample of data (utilized in studies by Woody *et al.*, Cottler, and Hale *et al.*)[380] is derived from a population studied during the Substance Abuse Disorders Field Trials for DSM-IV. This sample population came from five sites around the United States

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[379] Department of Health and Human Services, Public Health Service, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, *Reducing the Health Consequences of Smoking—25 Years of Progress, a Report of the Surgeon General* (Atlanta: 1989), at 295. *See* AR (Vol. 130 Ref. 1593).

[380] Woody GE, Cottler LB, Cacciola J, Severity of dependence: data from the DSM-IV field trials, *Addiction* 1993;88:1573-1579. *See* AR (Vol. 13 Ref. 150).

Cottler L, Comparing DSM-III-R and ICD-10 substance use disorders, *Addiction* 1993;88:689-696. *See* AR (Vol. 13 Ref. 149).

Hale KL, Hughes JR, Olivero AH, Helzar JE, Higgins ST, Bickel WK, Cottler LB, Nicotine dependence in a population-based sample, in *Problems of Drug Dependence, 1992*, NIDA Research Monograph 132, (Washington DC: Government Printing Office, 1993). *See* AR (Vol. 39 Ref. 60).

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and ranged in age from 18 to 44 years. Some of the subjects were from the general population, and others were selected, by a random digit dialing method, from subjects treated for substance abuse. Three separate analyses, using different assumptions and methods, were performed on these data, and the estimates of nicotine dependence reported in three published articles ranged from 77% to 92%. There is no evidence that these rates of nicotine dependence in these sample populations are greater than those for a nonpredisposed population that smoked for the same period. Indeed, the population of non–drug-abusing middle-aged men studied by Hughes *et al.* had a rate of nicotine dependence that was consistent with, and even higher than, the rates found in the Woody *et al.*, Cottler, and Hale *et al.* studies.

One study of nicotine addiction rates cannot be used to establish the prevalence of nicotine addiction because the population examined was not representative of the spectrum of smokers. The sample population in this study by Breslau *et al.* consisted of 394 smokers 21 to 30 years of age who were randomly selected from a well-defined population in a health maintenance organization (HMO).[381] The median age was 26 years, and 51% of the smokers were addicted to nicotine. These studies reflect that rates of dependence on nicotine increase substantially with duration of exposure and with the smoker's age: Although 51% of these young smokers were dependent on nicotine, fully 90% of the middle-aged smokers in the study by Hughes *et al.* were dependent on nicotine. Moreover, Breslau *et al.* acknowledge that the rate of dependence found in this sample of young smokers may not be representative of the rate among all smokers.

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[381] Breslau N, Kilbey MM, Andreski MA. Nicotine dependence, major depression, and anxiety in young adults. *Archives of General Psychiatry* 1991;48:1069-1074. *See* AR (Vol. 37 Ref. 17).

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In conclusion, the studies relied on by FDA were not chosen in a preferentially selected manner, but on the basis of study design and methodological considerations. The data sets reflect populations that can be considered representative of cross sections of the U.S. smoking population. There is no evidence to suggest that these studies are not generalizable to the population of smokers. FDA believes that these studies support the claim that 75% to 90% of smokers consume cigarettes to satisfy nicotine addiction. Comments of the American Psychiatric Association agree with this assessment, stating that "DSM based studies . . . found that 80%-90% of adult smokers are nicotine dependent."[382]

2. The tobacco industry argues that dependence can never be measured in a large population. This contention is disproved by the successful population-based studies just described. The industry's comments were premised on selective quotations from researchers, none of whom were actually agreeing with the assertion that all such studies are impossible or invalid.

3. The tobacco industry criticizes the data collection methods in the population studies FDA relied upon to support tobacco dependence rates. The industry argues that self-reporting results in inaccurate conclusions and cites an article by Kozlowski *et al.* to support this contention.[383]

FDA disagrees. This method of data collection is a scientifically recognized and accepted mode of inquiry for prevalence studies and is relied upon to determine the

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[382] American Psychiatric Association, Comment (Jan. 2, 1996), at 2. *See* AR (Vol. 700 Ref. 1020).

[383] Kozlowski LT, Herman CP, Frecker RC, What researchers make of what cigarette smokers say: filtering smokers' hot air, *Lancet* 1980;1(8170):699-700. *See* AR (Vol. 535 Ref. 96, vol. III.I).

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population prevalence of other disorders, including alcohol dependence, cocaine dependence, and depression.[384] Some of these are disorders for which, compared to tobacco use, interview methods would be less likely to reveal accurate results because of the criminal consequences associated with illicit drug use. Moreover, agencies that have expertise in tracking the prevalence of disease in this country, such as the Centers for Disease Control and Prevention, rely on such studies.[385] The tobacco industry itself cites multiple surveys based on self-reporting in its comments.

The industry also mischaracterizes the article by Kozlowski *et al.* The article does not support the industry's argument that all self-reported data in population studies are inaccurate. In the article, the authors suggest that self-reports of abstinence among people quitting smoking may be inflated. The authors do not suggest that any other information obtained by self-reporting is unreliable, nor do they give any reason to extrapolate their observations to reporting of other information about smoking behavior. Finally, despite their belief that some smokers may exaggerate the number and success of their attempts at abstinence, the authors never doubt that a large proportion of smokers try to quit.

Accordingly, FDA concludes that the methods used in the population prevalence studies are accepted and reliable.

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[384] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 175-272. See AR (Vol. 535 Ref. 96, vol. III.B).

[385] *See, e.g.*, Centers for Disease Control and Prevention, Reasons for tobacco use and symptoms of nicotine withdrawal among adolescents and young adult tobacco users—United States, 1993, *Morbidity and Mortality Weekly Report* 1994;43(41):745-750. *See* AR (Vol. 43 Ref. 162).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

c. **Comments on Tobacco Use for Effects on Mood and Weight**

1. The tobacco industry contends that FDA has not established that consumers use cigarettes or smokeless tobacco nearly exclusively either to affect mood or to control weight. According to the comment, the studies cited by FDA do not show that a high percentage of consumers use tobacco to affect mood or control weight and that there are an insufficient number of such studies upon which to base a conclusion.

This comment misinterprets the standard for establishing that a product is "intended to affect the structure or any function of the body" through consumer use. As noted in section II.B.1., above, some courts have suggested that where the Agency relies solely on consumer use to establish intended use, consumers must use the product predominantly or nearly exclusively for pharmacological purposes. These cases contain no requirement, however, that consumers use the product in question nearly exclusively for *each* individual pharmacological effect the product produces. Thus, there is no requirement that consumers use nicotine nearly exclusively for each of its pharmacological effects. It is sufficient to establish that consumers as a group use tobacco to obtain any of the several effects on structure or function sought by consumers (for example, to satisfy addiction, for other psychoactive effects, and to control weight). *See ASH v. Harris*, 655 F.2d at 240; *NNFA v. Mathews*, 557 F.2d at 334-336.

FDA also disagrees that there are insufficient studies to support the conclusion that consumers use tobacco to affect mood and control weight. The many studies cited by FDA conclusively show that the majority of tobacco consumers rely on tobacco products to achieve a relaxing or calming effect. *See* Jurisdictional Analysis, 60 FR 41579–41580.

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For example, one survey found that over 60% of smokers aged 16 to 44 believe that smoking reduces nervous irritation.[386]

The use of cigarettes for weight control is similarly established in numerous studies. These studies show that smokers believe that smoking keeps weight down and that weight control is a significant motivation to continue smoking. The Surgeon General's 1988 Report on Nicotine Addiction reviewed a large number of studies demonstrating that weight control is a powerful motivator for initiation and maintenance of smoking in as many as one-third to one-half of young smokers.[387]

d. Comments on Nonpharmacological Factors Associated with Tobacco Use

1. The tobacco industry quotes several addiction experts stating that there are social, emotional, and behavioral variables that explain patterns of tobacco use. The industry concludes that consumers do not use tobacco products "nearly exclusively" for the pharmacological effects of nicotine.

FDA disagrees. The industry confuses the details of tobacco use with the reason for use. While multiple factors may explain why a particular person decides to smoke a particular cigarette at a particular moment, data support only one reason why the vast majority of consumers use tobacco products day after day, year after year: to obtain the drug effects of nicotine.

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[386] McKennell AC. Smoking motivation factors. *British Journal of Social and Clinical Psychology* 1970;49(1):8-22. *See* AR (Vol. 13 Ref. 152-1).

[387] Surgeon General's Report, 1988, at 438-439. *See* AR (Vol. 129 Ref. 1592).

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Indeed, the scientific consensus holds that nonpharmacological factors are important to consumers only because they are linked to the pharmacological effects of nicotine. Thus, Jed Rose, one of the key researchers cited by the industry to support the contention that consumers use tobacco for nonpharmacological reasons, refers to nonpharmacological factors as "sensory cues" that are used to meter nicotine intake.[388]

As described in section II.B.3., above, such cues become "conditioned" as they are associated with the pharmacological effects of nicotine on the brain. These environmental factors are certainly important to tobacco consumers, as they are to users of other addictive drugs,[389] but they are not the primary reasons for use. As a tobacco industry executive in a speech to the company's board of directors said:

> [T]he psychosocial motive is not enough to explain continued smoking. Some other motive force takes over to make smoking rewarding in its own right. Long after adolescent preoccupation with self-image has subsided, the cigarette will even preempt food in times of scarcity on the smoker's priority list . . . We are of the conviction . . . that the ultimate explanation for the perpetuated cigarette habit resides in the pharmacological effect of smoke upon the body of the smoker, the effect being most rewarding to the individual under stress.[390]

2. The cigarette manufacturers cite research suggesting that nicotine-free cigarettes have flavor[391] and may help smokers to quit.[392] They draw particular attention

[388] Rose JE, Behm FM, Levin ED, Role of nicotine dose and sensory cues in the regulation of smoke intake, *Pharmacology, Biochemistry and Behavior* 1993;44:891-900. *See* AR (Vol. 8 Ref. 100).

[389] Surgeon General's Report, 1988, at 59. *See* AR (Vol. 129 Ref. 1592).

[390] Wakeham H (Philip Morris, Inc.), *Smoker Psychology Research*, presented to Philip Morris board of directors (Nov. 26, 1969), at 237, 240. *See* AR (Vol. 11 Ref. 142).

[391] Levin ED, Behm FM, Rose JE, The use of flavor in cigarette substitutes, *Drug and Alcohol Dependence* 1990;26:155-160, at 159. *See* AR (Vol. 535 Ref. 96, III.J).

[392] Butschky MF, Bailey D, Henningfield JE, Pickworth WB, Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers, *Pharmacology, Biochemistry and Behavior* 1995;50(1):91-96. *See* AR (Vol. 442 Ref. 7484).

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to a recent presentation by Rose *et al.*, in which smokers given a denicotinized cigarette reported the same or slightly less relief of craving than smokers given intravenous nicotine, and less relief than smokers given their usual brand of cigarettes.[393] They also reported more immediate satisfaction from the denicotinized cigarette than from intravenous nicotine, although less than from their usual brand. The denicotinized cigarette provided less psychological reward than did intravenous nicotine. The smokeless tobacco manufacturers also suggest that no-nicotine substitutes for smokeless tobacco may have helped some users remain abstinent. According to the industry, this research demonstrates that consumers use tobacco products for reasons other than nicotine.

FDA disagrees. The cited studies do suggest that low- or no-nicotine products can be used in research and in a small proportion of former users of tobacco products. Yet the products have been uniformly rejected *by tobacco consumers*, who do not view them as acceptable substitutes for cigarettes. When given a choice, tobacco users will not abandon nicotine for flavor, demonstrating the real reason they smoke. For example, Next, a denicotinized cigarette that was briefly marketed by Philip Morris, was removed from the market because, according to the company, it was not accepted by consumers.

The cited studies replicate many others that show that the most consistent and strongest effects are produced by nicotine-delivering cigarettes. It is not surprising that nicotine injections, which, according to the studies produced significant pain and burning at the site of injection, do not produce all the satisfaction of smoking nor duplicate the

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[393] Rose JE, Westman EC, Behm FM. Comparative effects of intravenous nicotine and de-nicotinized cigarette smoke, poster presented at the annual meeting of the Society for Research on Nicotine and Tobacco (Mar. 15-17, 1996), Washington, D.C. *See* AR (Vol. 711 Ref. 21).

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taste and throat sensations of smoking. As described in section II.B.3., above, the efficacy of nicotine-free cigarettes in alleviating some of the symptoms of withdrawal is consistent with the conclusion that social and environmental factors become associated with obtaining the pharmacological effects of nicotine, and thus are perceived as pleasurable as a "conditioned response," but in and of themselves are not the reason people smoke. Low- or no-nicotine cigarettes may temporarily provide some relief to consumers as a result of the conditioned response to the sensorimotor aspects of smoking, but this response is subject to "rapid extinction" when nicotine is withheld.[394] This phenomenon is similar to the temporary finding that heroin addicts feel pleasure from injecting themselves with saline.[395]

The study by Rose is entirely consistent with these findings. The study evaluated only the immediate effects of a denicotinized cigarette on craving reduction, satisfaction, and psychological reward. It did not attempt to evaluate any effects of denicotinized cigarettes on sustained satisfaction or relief of withdrawal symptoms. Rose himself has stated that smokers seek the sensory cues of smoking because "the repetition of the smoking act thousands of times per year by a moderately heavy smoker leads to a strong conditioned association between the sensory aspects of smoking . . . and the pharmacological effects of nicotine."[396] Therefore, according to Rose, "effective

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[394] *Id.*

[395] O'Brien CP, Testa T, Ternes J, Greenstein R. Conditioning effects of narcotics in humans, in *Behavioral Tolerance: Research and Treatment Implications*. NIDA Research Monograph 18 (Washington DC: Government Printing Office No. 017-024-00899-8, Jan. 1978), at 67-71. *See* AR (Vol. 535 Ref. 98, vol. III.L).

[396] Rose JE, Levin ED. Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking, *British Journal of Addiction* 1991;86:605-609, at 605. *See* AR (Vol. 67 Ref. 58).

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treatment of tobacco abuse needs to take into account the influence of these sensory cues,"[397] by, for example, providing the smoker with de-nicotinized cigarettes, in addition to strategies to eliminate nicotine dependency.[398] He is explicit, however, that nicotine is the primary reinforcer of smoking behavior, and that desire for the sensory aspects of tobacco use is the result of conditioned reinforcement maintained by nicotine's primary reinforcement.[399]

3. To support the argument that consumers use tobacco products for flavor, the tobacco industry cites research in which smokers' satisfaction with smoking decreased when their upper airways were anesthetized.

Upon review of this research, FDA finds that the studies do not support the contention that consumers smoke cigarettes primarily for flavor. As described above, the researcher who led the study, Rose, believes that nonpharmacological factors associated with tobacco consumption are "cues" important to smokers only by association with nicotine's pharmacological impact.

Moreover, the research cited does not establish that the reason for the drop in smoking satisfaction upon airway anesthetization was the blockade of sensory input from smoke. These decreases in satisfaction might have been due simply to the unpleasant sensation of upper airway anesthetization, not to any blockade of sensory input from smoke. In this study, satisfaction with "sham smoke" also dropped with anesthesia. Sham smoke was so diluted as to provide few pharmacological or sensory effects. Thus,

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[397] *Id.*

[398] *Id.* at 607.

[399] *Id.* at 605-606.

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providing anesthesia decreased the satisfaction of consuming real cigarette smoke *and placebo smoke.*[400]

The study does, however, provide data addressing the importance of the pharmacological aspects of smoking. Thirty minutes after smoking, the subjects who had received smoke delivering nicotine—*regardless of whether their throats had been anesthetized*—felt similarly satisfied. And their satisfaction was greater than that of those who had received "sham smoke." Thus, the study indicated that nicotine produces smoking satisfaction *even in the absence of mouth and throat sensation.*

4. The tobacco industry cites three studies to support the argument that consumers use tobacco products out of "habit and ritual."

Upon review of these studies, FDA concludes that they provide no evidence that "habit and ritual" are the primary motivation for use of tobacco products. As described at length above, "habit and ritual" are important to consumers of all addictive drugs, but only through their linkage to the pharmacological effects of the drug.

First, the industry cites a study in which some smokers did not consider the first cigarette of the day their favorite.[401] The observation relates to a detail of smoking rather than to underlying motivation; as described in section II.B.3., above, there are many reasons why an individual may desire a particular cigarette at a particular time. This is not evidence that "habit or ritual" is the driving biological force for maintenance of tobacco use.

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[400] Rose JE, Tashkin DP, Ertis A, Zinser MC, Lafer R, Sensory blockade of smoking satisfaction, *Pharmacology, Biochemistry and Behavior* 1983;23:289-293, at 290 (emphasis added). *See* AR (Vol. 42 Ref. 124).

[401] Jarvik M, Killen JD, Varady A, Forumann SP, The favorite cigarette of the day. *Journal of Behavioral Medicine* 1993;16:413-422. *See* AR (Vol. 535 Ref. 96, III.A).

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The industry then quotes the speculative conclusion of a study without any description of the research. In fact, the study's main finding was that the smell of cigarettes was *not* important for smoking behavior.[402]

The industry cites another conclusion of a study without any description of the research.[403] One of the study's major findings was that enforced abstinence (smokers were not allowed to smoke for an afternoon) had different effects on subsequent smoking behavior than natural abstinence (smokers did not smoke while asleep at night). Basic biological imperatives undoubtedly affect the details of smoking behavior but certainly cannot explain the reason for tobacco use.

5. The tobacco industry argues that the "social aspects" of smoking explain consumer use of tobacco. No studies are cited to support this conclusion. As the Surgeon General's Report noted in 1988, social factors influence initiation and patterns of use of many addictive drugs;[404] the primary reason for the drug's use, however, is pharmacological. In this respect, nicotine is similar to heroin.[405]

6. The smokeless tobacco industry argues that the evidence cited by FDA in support of its conclusion that consumers use tobacco products nearly exclusively for pharmacological effects has little to do with smokeless tobacco. Five studies were

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[402] Baldinger B, Hasenfratz M, Battig K. Switching to ultralow nicotine cigarettes: effects of different tar yields and blocking of olfactory cues, *Pharmacology, Biochemistry and Behavior* 1995;50(2):233-239, at 238. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[403] Jacober A, Hasenfratz M, Battig K. Cigarette smoking: habit of nicotine maintenance? *Human Psychopharmacology* 1994;9:117-123, at 117. *See* AR (Vol. 535 Ref. 96, vol. III.G).

[404] Surgeon General's Report, 1988, at 15. *See* AR (Vol. 129 Ref. 1592).

[405] Jaffe JH, Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522–573), at 529. *See* AR (Vol. 535 Ref. 96, vol. III.G).

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submitted with the comment that are claimed to demonstrate that smokeless tobacco consumers use those products because they "enjoy the taste" or simply "like it," not for any "pharmacological effects."[406]

FDA disagrees with the industry's interpretation of these studies. As discussed in section II.B.3., above, when people use drugs with powerful pharmacological effects such as nicotine they commonly associate many environmental stimuli with the pleasurable experience of consuming the substance. Thus, a survey result that consumers "enjoy the taste" indicates only that a significant portion of consumers have linked the sensory cues to the pharmacological effects of nicotine.

None of the five studies cited by the industry noted whether users who did not give pharmacological reasons for using smokeless tobacco had ever tried to quit. Thus, many of these users may not have been aware of their pharmacological addiction. As an expert quoted by the Inspector General of the Department of Health and Human Services

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[406] Walsh MM, Hilton JF, Ernster VL, Mastoredis CM, Grady DG, Prevalence, patterns, and correlates of spit tobacco use in a college athlete population, *Addictive Behavior* 1994;19:411-427. *See* AR (Vol. 526 Ref. 95, vol. VIII).

Lopez LC, Smokeless tobacco consumption by Mexican-American university students, *Psychology Reports* 1994;75:279-284. *See* AR (Vol. 526 Ref. 95, vol. VIII).

Glover ED, Laflin M, Flannery D, Albritton DL, Smokeless tobacco use among American college students, *Journal of American College Health* 1989;38:81-84. *See* AR (Vol. 526 Ref. 95, vol. VII).

Wisniewski JF, Bartolucci AA, Comparative patterns of smokeless tobacco usage among major league baseball personnel, *Journal of Oral Pathology and Medicine* 1989;18:322. *See* AR (Vol. 526 Ref. 95, vol. VIII).

Connolly GN, Orleans GT, Kogan M, Use of smokeless tobacco in major-league baseball, *New England Journal of Medicine* 1988;318(19):1281-1285. *See* AR (Vol. 526 Ref. 95, vol. VII).

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explained, "Many haven't tried to quit. But when we tell them the health consequences, and then they try to quit, they can't."[407]

In studies cited by the industry, some users of smokeless tobacco stated that they "enjoy the taste," but a significant percentage of these users also reported that they use smokeless tobacco for psychological reasons. For example, in one study, a majority of 195 users of snuff and chewing tobacco reported using tobacco for one or more pharmacological effects, including relieving stress, relief of "strong cravings," and relieving the discomfort of withdrawal.[408] These statements support the conclusion that the majority of people who use smokeless tobacco do so for the well-established pharmacological effects of nicotine: stimulation, sedation, and addiction. These studies thus constitute additional evidence that smokeless tobacco is primarily used by consumers to obtain the pharmacological effects of nicotine.

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[407] Department of Health and Human Services, Office on Smoking and Health, *Spit Tobacco and Youth* (Washington DC: Government Printing Office, 1992), at 8. *See* AR (Vol. 7 Ref. 76).

[408] Walsh MM, Hilton JF, Ernster VL, Masouredis CM, Grady DG, Prevalence, patterns, and correlates of spit tobacco use in a college athlete population, *Addictive Behavior* 1994;19:411-427. *See* AR (Vol. 526 Ref. 95, vol. VIII).

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C. THE STATEMENTS, RESEARCH, AND ACTIONS OF THE CIGARETTE MANUFACTURERS SHOW THAT THE MANUFACTURERS INTEND THEIR PRODUCTS TO AFFECT THE STRUCTURE AND FUNCTION OF THE BODY

In sections II.A. and II.B., above, the Agency has concluded that cigarettes and smokeless tobacco are intended to affect the structure and function of the body on the basis of the foreseeable pharmacological effects and uses of cigarettes and smokeless tobacco and the widespread actual use of cigarettes and smokeless tobacco by consumers for pharmacological purposes. In this section, the Agency considers another category of persuasive evidence of intended use: the statements, research, and actions of the cigarette manufacturers themselves. In section II.D., below, the Agency considers the statements, research, and actions of the smokeless tobacco manufacturers.

The administrative record includes extensive evidence of the cigarette manufacturers' statements, research, and manufacturing practices. Much of this evidence has only recently become available as a result of the Agency's investigation, congressional hearings, and other investigations and sources. This evidence is part of the relevant objective evidence that the Agency may consider in determining the manufacturer's "intended uses" of a product.

In the Jurisdictional Analysis, the Agency made extensive findings based on the evidence then available regarding the statements, research, and actions of the cigarette manufacturers. FDA received comments on these findings from the individual tobacco companies and tobacco industry trade associations, as well as from public health organizations and other interested groups and members of the public. After careful consideration of the evidence in the record and the public comments, the Agency finds that

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the evidence described in this section provides a third independent basis for concluding that cigarettes are in fact intended to affect the structure and function of the bodies of smokers.

In section II.C.1., FDA discusses its legal authority to consider evidence of the manufacturers' statements, research, and actions in establishing intended use. This discussion shows that an intent to affect the structure or function of the body can be established by evidence showing that (1) the manufacturer "has in mind" that the product will be used by consumers for pharmacological purposes, or (2) the manufacturer has "designed" the product to provide pharmacological effects. The Agency's role in making these determinations is that of a fact finder. It weighs the statements, research, and actions of the manufacturer to determine the particular uses the manufacturer has in mind or designs its product to provide.

The Agency's fact-finding task has been made more difficult by the manufacturers' general refusal to cooperate with the Agency's investigation. Although some manufacturers did permit FDA investigators to visit their manufacturing plants in the spring of 1994, the manufacturers have failed to provide FDA with information and documents requested by FDA in July 1994 regarding nicotine in cigarettes.[409] In particular, the manufacturers have failed to comply with FDA's request for company documents regarding the pharmacological effects of nicotine and the role of nicotine in cigarette design and manufacturing. The limited number of company documents provided

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[409] *See, e.g.*, Letter from Chesemore RG (FDA) to Bible GC (Philip Morris Inc.) (Jul. 11, 1994). *See* AR (Vol. 54 Ref. 617). Similar letters were sent to other cigarette and smokeless tobacco manufacturers.

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by the manufacturers with their comments sheds little light on the role of nicotine in cigarettes and does not significantly change the evidence in the record.

The Agency's discussion of the evidence of the manufacturers' statements, research, and actions is divided into several parts. In section II.C.2., the Agency discusses the statements and research of each of the major cigarette companies and the Council for Tobacco Research, a trade association to which they belong. This evidence shows that the manufacturers have known for decades that nicotine has the characteristics of addictive drugs and causes other significant pharmacological effects and that consumers use cigarettes primarily to obtain the pharmacological effects of nicotine, including satisfaction of their addiction. This evidence also shows that in internal discussions, senior researchers for the cigarette manufacturers refer to cigarettes as drug delivery systems, calling them a "dispenser for a dose unit of nicotine,"[410] a vehicle for delivery of nicotine,"[411] and other similar terms. This evidence is sufficient by itself to establish that cigarettes are intended to affect the structure and function of the body, because it shows that the manufacturers "have in mind" that their products will be used specifically for pharmacological purposes.

In sections II.C.3. and II.C.4., the Agency discusses the second basis for determining the manufacturers' intent through their statements, research, and actions—namely, the evidence that manufacturers have "designed" cigarettes to provide pharmacologically active doses of nicotine to consumers. In section II.C.3., the Agency discusses the product research and development activities of the manufacturers. This

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[410] Dunn WL (Philip Morris Inc.), *Motives and Incentives in Cigarette Smoking* (1972), at 5. *See* AR (Vol. 12 Ref. 133).

[411] Teague CE (R.J. Reynolds Tobacco Co.), *Research Planning Memorandum on The Nature of the Tobacco Business and the Crucial Role of Nicotine Therein* (Apr. 14, 1972), at 1. *See* AR (Vol. 531 Ref. 125).

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evidence shows that the manufacturers have conducted extensive product research and development to establish the dose of nicotine necessary to produce pharmacological effects and to optimize the delivery of nicotine to consumers.

In section II.C.4., the Agency discusses the evidence that the manufacturers do in fact manipulate and control nicotine deliveries in their commercial cigarettes. This evidence supports a finding that the manufacturers manipulate and control the delivery of nicotine in commercial cigarettes to provide a pharmacologically active dose of nicotine to consumers. Taken together, the evidence in sections II.C.3. and II.C.4. establishes yet another basis for finding that cigarettes are intended to affect the structure and function of the body.

In section II.C.5., the Agency concludes that, when considered cumulatively, the evidence from the statements, research, and actions of the manufacturers is internally consistent and mutually corroborating, further supporting the finding that the effects of cigarettes on the structure and function of the body are "intended" by the manufacturers. Finally, in section II.C.6., the Agency responds to substantive comments concerning the evidence of the manufacturers' statements, research, and actions that are not addressed in sections II.C.2. to II.C.5.[412]

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[412] The discussion of the statements, research, and actions of the manufacturers in this section cites hundreds of documents. It is the totality of the evidence from these documents that the Agency relies upon. No single document cited by the Agency is essential to the Agency's conclusion in section II.C. that the manufacturers intend their products to affect the structure and function of the body. In particular, although considerable evidence of the statements, research, and actions of the manufacturers was submitted to the Agency after the publication of the Jurisdictional Analysis on August 11, 1995, none of this evidence is essential to the Agency's finding of intended use in section II.C. The new evidence is summarized below because it provides persuasive corroboration that the cigarette manufacturers do intend to affect the structure and function of the body. However, the Agency would reach the same conclusions regarding the intent of the manufacturers even without this additional evidence. In addition, none of the documents in the Agency's docket of confidential documents is essential to the Agency's determination. *See* AR (Vol. 505-518).

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1. "Intended Use" May Be Established on the Basis of the Statements, Actions, and Research of the Manufacturers

Reliance on the statements, research, and actions of manufacturers to establish intended use is consistent with the plain language of the statute. The statute provides that products "intended" to affect the structure or any function of the body are drugs or devices. Sections 201(g)(1)(C) and 201(h)(3). According to a canon of statutory construction, words used by Congress, unless otherwise defined, will be interpreted as taking their ordinary meaning. *See, e.g., Smith v. United States*, 508 U.S. 223, 228 (1993); *Chevron v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 860 (1984). In this case, the ordinary meaning of "intend" includes "to have in mind" and "to design" for a particular use. These plain meanings allow the Agency to consider the manufacturer's statements, research, and actions in determining intended use.

The *American Heritage Dictionary*, for instance, defines "intend" as: "1. To have in mind; plan. 2.a. To design for a specific purpose. b. To have in mind for a particular use. . . ."[413] Consistent with this meaning, the Agency interprets "intended" uses to include those specific uses that are "in the mind" of the manufacturer or for which the manufacturer "designs" the product. The plain meaning of the statute thus permits the Agency to inquire into the statements, research, and actions of the manufacturer. What the manufacturer says in internal documents, the kind of research the manufacturer conducts, and the actions of the manufacturer in producing its product can all be evidence

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[413] *The American Heritage Dictionary of the English Language*, 2d ed. (Boston: Houghton Mifflin Co., 1991), 668. *See* AR (Vol. 526 Ref. 95, vol. V). Other dictionary definitions are similar. *See, e.g., Webster's New World Dictionary of American English*, 3d college ed. (New York: Simon & Schuster, Inc., 1988), 702 ("intend 1. *to have in mind as a purpose*; plan 2. to mean (something) to be *or be used (for): design. . . .*") (emphasis added).

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of the particular uses the manufacturer has in mind or for which the manufacturer has designed the product.

FDA's regulations on the meaning of "intended uses" are consistent with the statutory language and explicitly contemplate that FDA may examine the knowledge, actions, and expressions of manufacturers and other vendors. 21 CFR 201.128 and 801.4. These regulations state that intended uses are to be established on the basis of "objective intent." FDA's "objective intent" standard means that the Agency may consider objective evidence to determine a manufacturer's intent, notwithstanding the manufacturer's assertions that pharmacological effects and uses are not intended. As the courts have recognized, "FDA is not bound by the manufacturer's subjective claims of intent but *can find actual therapeutic intent on the basis of objective evidence.*" *NNFA v. Mathews*, 557 F.2d at 334 (emphasis added); *accord United States v. Storage Spaces Designated Nos. "8" and "49,"* 777 F.2d 1363, 1366 n. 5 (9th Cir. 1985) ("self-serving labels cannot be used to mask true intent"), *cert. denied*, 479 U.S. 1086 (1987).

The regulations recognize that as a fact finder, FDA may consider a broad range of evidence of intended use, including evidence of the statements, research, and actions of the manufacturer. For example, the regulations state that "the objective intent is determined by such persons' *expressions . . . or oral or written statements.*" 21 CFR 201.128 (emphasis added). These "expressions" and "oral or written statements" can include relevant and probative intracompany memoranda or research.

Indeed, the regulations provide express authority for FDA to consider evidence of the manufacturer's actual intent. The regulations state that "objective intent . . . may be shown by the circumstances that the article is, *with the knowledge of [the manufacturer]*,

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offered and used for a purpose for which it is neither labeled nor advertised." *Id.* (emphasis added). The regulations also direct FDA to consider circumstances in which the manufacturer "*knows*, or *has knowledge of facts* that would give him notice" that a product is to be used for purposes other than those expressly promoted by the manufacturer. *Id.* (emphasis added). Proving whether a manufacturer "knows" or has "knowledge of facts that would give him notice" of pharmacological uses of a product can include an inquiry into the actual understanding of the manufacturer, including consideration of the statements, research, and actions that may be probative of the manufacturer's actual knowledge.

Moreover, the regulations provide that objective intent may be shown by the "*circumstances surrounding the distribution of the article.*" *Id.* (emphasis added). This broad phrase allows the fact finder to infer the intended uses of a product based on, among other factors, the conduct of the manufacturer that occurs prior to distribution. For example, evidence that shows how distributed tobacco products are designed and formulated is reasonably considered a "circumstance surrounding distribution of the article."

Courts have also recognized that the Agency may consider "objective evidence" to determine a manufacturer's intent. *See NNFA v. Mathews*, 557 F.2d at 334; *United States v. Storage Spaces*, 777 F.2d at 1366; *Latex Surgeons' Gloves*, 799 F. Supp. at 1295 (circumstances surrounding manufacture and distribution of product demonstrated intended use despite manufacturer's claim to FDA that product was not a device); *Hanson*, 417 F. Supp. at 35 (statements by plaintiff distributors and importers that drug was needed by patients to treat cancer is relevant to intended use).

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The Agency's role in determining intended use on the basis of the statements, research, and actions of the manufacturer is that of a fact finder. The Agency's responsibility is to reach the best factual judgments it can from the record of the statements, research, and actions before it, including evidence submitted during the comment period.

2. The Cigarette Manufacturers Understand That Nicotine Has Addictive and Other Pharmacological Effects and That Smokers Use Cigarettes To Obtain These Effects

As discussed below, the evidence in the record shows that the cigarette manufacturers have extensive knowledge of effects of nicotine on smokers. The manufacturers know that nicotine has the characteristics of other addictive drugs; that it provides other significant pharmacological effects; and that it is the primary reason that smokers use cigarettes. This evidence establishes that when the manufacturers offer cigarettes to the public, they "have in mind" that their cigarettes will be used by smokers to obtain the pharmacological effects of nicotine. This evidence is thus sufficient by itself to establish that the manufacturers intend the pharmacological uses of their products.

a. The Statements and Research of Philip Morris

The administrative record includes over three decades of internal statements and research on nicotine by Philip Morris, the nation's largest cigarette manufacturer. These documents indicate that senior researchers and officials at Philip Morris have long viewed nicotine as a "powerful pharmacological agent"[414] and "the primary reason"[415] people

[414] Charles JL (Philip Morris Inc.), *Nicotine Receptor Program-University of Rochester* (Mar. 18, 1980), in 141 Cong. Rec. M7680 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[415] Philip Morris Inc., Draft Report Regarding a Proposal for a "Safer" Cigarette, Code-named *Table*, at 1. *See* AR (Vol. 531 Ref. 122).

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smoke. This knowledge shows that Philip Morris understands that its product will affect the structure and function of the body and will be used by consumers for these drug effects.

i. The Views of Senior Researchers and Officials. Philip Morris officials recognized the importance of the pharmacological effects of nicotine in cigarettes as early as 1961. That year, Helmut Wakeham, a senior Philip Morris research scientist, informed the company's research and development committee that "nicotine is believed essential to cigarette acceptability."[416] Wakeham also explained the pharmacological effects of nicotine, stating that "low nicotine doses stimulate, but high doses depress functions" and that nicotine contributes to the "pleasurable reactions or tranquillity" produced by smoking.[417]

By 1969, the views of the Philip Morris scientists on the pharmacological effects of cigarettes were communicated to the Philip Morris board of directors. During that year, Wakeham, who was then vice president for research and development, briefed the Philip Morris board of directors on why people smoke. He expressed his department's "conviction" that "the ultimate explanation for the perpetuated cigaret habit resides in the pharmacological effect of smoke upon the body of the smoker." He further stated that smokers' craving for cigarettes is so strong that "the cigaret will even preempt food in times of scarcity":

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Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 6. *See* AR (Vol. 638 Ref. 2).

[416] Wakeham H (Philip Morris Inc.), *Tobacco and Health—R&D Approach* (Nov. 15, 1961), at 43. *See* AR (Vol. 125 Ref. 1314).

[417] *Id.* at 40.

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> [T]he psychosocial motive is not enough to explain continued smoking. Some other motive force takes over to make smoking rewarding in its own right. Long after adolescent preoccupation with self-image has subsided, the cigaret will even preempt food in times of scarcity on the smoker's priority list. . . . The question is "Why?"
>
> . . . .We are of the conviction, . . . that the ultimate explanation for the perpetuated cigaret habit resides in the pharmacological effect of smoke upon the body of the smoker, the effect being most rewarding to the individual under stress.[418]

Wakeham's views on the central importance of the "pharmacological effect" of nicotine were shared by other senior researchers and officials at Philip Morris, as the following examples demonstrate:

- In 1972, Philip Morris scientist William Dunn characterized cigarettes as a nicotine delivery system in the following language:

> Think of the cigarette pack as a storage container for a day's supply of nicotine. . . .
>
> *Think of the cigarette as a dispenser for a dose unit of nicotine. . . .*
>
> Think of a puff of smoke as the vehicle of nicotine . . . .
>
> *Smoke is beyond question the most optimized vehicle of nicotine and the cigarette the most optimized dispenser of smoke.*[419]

- In 1974, Philip Morris' director of research, Thomas Osdene, who subsequently became vice president for science and technology, approved and sent to Wakeham and other senior Philip Morris officials a report that analogized smoking to drug use. The report's "working hypothesis" is that "[d]ose-control continues even after the puff of smoke is drawn into the mouth." The report postulates that the consumer regulates

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[418] Wakeham H (Philip Morris Inc.), *Smoker Psychology Research*, presented to Philip Morris board of directors (Nov. 26, 1969), at 237, 240. *See* AR (Vol. 11 Ref. 142).

[419] Dunn WL (Philip Morris Inc.), *Motives and Incentives in Cigarette Smoking* (1972), at 5-6 (emphasis added). *See* AR (Vol. 12 Ref. 133).

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smoke intake "to achieve his habitual quota of the pharmacological action," and notes that if smokers deprived of cigarettes display an increase in aggression, it may be explained as "the emergence of reactions . . . not unlike those to be observed upon withdrawal from any of a number of habituating pharmacological agents."[420]

- In 1976, Philip Morris researcher A. Udow wrote a memorandum on "Why People Start To Smoke." The memorandum observes that once people start to smoke, one of the reasons they will continue to smoke is that cigarettes serve as "*a narcotic, tranquilizer, or sedative.*"[421]
- In 1978, the authors of Philip Morris' 5-year plan for research and development stated that "*nicotine may be the physiologically active component of smoke having the greatest consequence to the consumer.*"[422]
- In 1980, Philip Morris researcher Jim Charles, who subsequently became vice president for research and development, wrote the then vice president for research and development, Robert Seligman, that:

> *Nicotine is a powerful pharmacological agent with multiple sites of action and may be the most important component of cigarette smoke. Nicotine and an understanding of its properties are important to the continued well being of our cigarette business since this alkaloid has been cited often as "the reason for smoking."*. . . Nicotine is known to have effects on the central and

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[420] Philip Morris Research Center, *Behavioral Research Annual Report, Part II* (Nov. 1, 1974) (approved by Osdene TS), in 141 Cong. Rec. H7658, H7660 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[421] Udow A (Philip Morris Inc.), *Why People Start to Smoke* (Jun. 2, 1976), in 141 Cong. Rec. H7664 (daily ed. Jul. 25, 1995) (emphasis added). *See* AR (Vol. 14 Ref. 175a).

[422] Philip Morris Inc., *Research and Development Five-Year Plan, 1979-1983* (Sep. 1978), in 141 Cong. Rec. H7668 (daily ed. Jul. 25, 1995) (emphasis added). *See* AR (Vol. 14 Ref. 175a).

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> peripheral nervous system as well as influencing memory, learning, pain perception, response to stress and level of arousal.[423]

A statement that the Agency received from a former Philip Morris research director, William Farone, expresses similar views. Farone was the director of applied research at Philip Morris from 1976-1984, during which period he supervised five divisions and 150 employees. According to Farone's statement:

> It is well recognized within the cigarette industry that *there is one principal reason why people smoke—to experience the effects of nicotine*, a known pharmacologically active constituent in tobacco. . . .
>
> . . . .
>
> *The strongly held conviction of most industry scientists and product developers was that nicotine was the primary reason why people smoked.*[424]

The administrative record contains many additional statements by Philip Morris researchers and officials acknowledging the significant pharmacological effects of nicotine and their importance to the smoker. *See, e.g.*, 60 FR 41584–41603, 41621–41667. Collectively, these statements show that Philip Morris' senior scientists and officials have known for decades that cigarettes function as a drug delivery system, providing the pharmacological effects of nicotine to consumers who smoke cigarettes for the primary purpose of obtaining these effects.

ii. Research into Nicotine Pharmacology. The foregoing views of Philip Morris' top research scientists and officials were based on extensive in-house research on

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[423] Charles JL (Philip Morris Inc.), *Nicotine Receptor Program-University of Rochester* (Mar. 18, 1980), in 141 Cong. Rec. H7680 (daily ed. Jul. 25, 1995) (emphasis added). *See* AR (Vol. 14 Ref. 175a).

[424] Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 1,6 (emphasis added). *See* AR (Vol. 638 Ref. 2).

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nicotine pharmacology. The studies conducted by Philip Morris ranged from traditional pharmacology involving animal experiments to EEG experiments.

Philip Morris conducted a large number of studies. In 1979 alone at least 16 different studies on nicotine pharmacology were conducted by three different research groups within Philip Morris' Behavioral Research Laboratory.[425] The Animal Behavior Group conducted six experiments on the drug effects of nicotine in rats. The Neuropsychology Laboratory conducted five experiments to determine the pharmacological effects of nicotine on the human brain, including experiments on "[t]he Effects of Cigarette Smoking on the Electroencephalogram" and "[L]ong-Term Smoke Deprivation and the Electrical Activity of the Brain."[426] The Smoking Behavior Group conducted studies on the behavioral consequences of smoking, including studies to determine the consequences of smoking low-nicotine cigarettes.

Beginning before 1980 and continuing until 1984, Philip Morris conducted research in search of a "nicotine analogue." This research demonstrates Philip Morris' knowledge that nicotine has the hallmark properties of a drug of abuse and shows the company's intention to preserve these properties in new products. As described by former Philip Morris scientist Victor DeNoble, the purpose of the research was "to come up with a molecule that would *mimic nicotine's effect in the brain*, and would not affect the peripheral nervous system and therefore not have cardiovascular liability."[427] Thus, while

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[425] Dunn WL (Philip Morris Inc.), *Plans and Objectives–1979* (Dec. 6, 1978), in 141 Cong. Rec. H7668-7670 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[426] *Id.* at H7669-7670.

[427] *Regulation of Tobacco Products (Part 2): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 33 (Apr. 28, 1994) (testimony of Victor DeNoble) (emphasis added). *See* AR (Vol. 708 Ref. 2).

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the company attempted to eliminate an adverse effect of nicotine, it deliberately sought to retain nicotine's effects on the brain.

To conduct this work, Philip Morris scientists had to identify and compare the pharmacological and behavioral effects of nicotine on the brain. The pharmacological and behavioral profiles of the nicotine analogues synthesized by Philip Morris chemists were then compared to those of nicotine.[428] Since the primary goal of the nicotine analogue program was to develop a nicotine analogue that would retain the physiological and behavioral effects of nicotine on the brain, especially its reinforcing properties, the newly synthesized nicotine analogues were screened in animal behavioral tests designed to assess their reinforcing properties. (A substance has reinforcing properties if it is able to induce repeated, compulsive use. *See* section II.A.3.c.i., above.) The tests used were "exactly the same tests" that the National Institute on Drug Abuse (NIDA) uses "to determine if a drug has an abuse potential."[429]

One of the principal NIDA tests used by Philip Morris was a series of "self-administration" experiments with rats. These studies determine addiction potential by assessing whether rats will press a lever to give themselves repeated injections of the test substance. There is a strong correlation between substances that are found to be self-

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[428] *Id.* at 5.

See also Declaration of Victor DeNoble of Feb. 2, 1995, at 2-9. *See* AR (Vol. 31 Ref. 524-5).

[429] *Regulation of Tobacco Products (Part 2): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 17 (Apr. 28, 1994) (testimony of Victor DeNoble). *See* AR (Vol. 708 Ref. 2).

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administered in rats and substances that are addictive in humans.[430] Philip Morris found that rats would self-administer nicotine.[431] According to the director of NIDA, "[t]hese findings from the DeNoble study indicate that nicotine has reinforcing properties, *one of the hallmark characteristics of an addictive drug*."[432] The Philip Morris researchers also found that rats would develop a tolerance to nicotine, another characteristic of an addictive drug.[433]

The senior management and top officials of Philip Morris "continually reviewed . . . and approved" this research.[434] In fact, in November 1983, the president of Philip Morris, Shep Pollack, visited the laboratory conducting the self-administration experiments and watched rats inject themselves with nicotine. Pollack was informed by the Philip Morris researcher in charge of the study, Victor DeNoble, that Philip Morris' self-administration studies followed "the exact procedure that NIDA would use to demonstrate abuse liability," and that the studies demonstrated that nicotine is "a reinforcing agent."[435] DeNoble further informed Pollack that although a finding of self-

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[430] Gardner EL., Brain reward mechanism, in *Substance Abuse, A Comprehensive Textbook*, 2d ed., eds. Lowinson JH, Ruiz P, Millman RB, *et al.* (Baltimore: Williams and Wilkins 1992), at 70. *See* AR (Vol. 8 Ref. 88).

See also section II.A.3.c.i.

[431] *Regulation of Tobacco Products (Part 2): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 5 (Apr. 28, 1994) (testimony of Victor DeNoble). *See* AR (Vol. 708 Ref. 2).

[432] *Id.* at 20 (letter from Leshner AI (NIDA) to Waxman HA (Apr. 13, 1994) (emphasis added)).

[433] *Id.* at 5 (testimony of Victor DeNoble). The Philip Morris researchers did not, however, find evidence of nicotine withdrawal.

[434] *Id.* at 5-6.

[435] *Id.* at 54.

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administration does not by itself prove that nicotine is addictive, it "predicts abuse liability."[436] Despite several attempts, DeNoble and his colleague Paul Mele were not allowed to publish the results of their self-administration studies or present their results at a meeting sponsored by the American Psychological Association.[437]

These studies were conducted for their potential commercial applicability. The memorandum describing the "plans and objectives" for the Behavioral Research Laboratory in 1979 states expressly that "the rationale for the program rests on the premise that such knowledge will strengthen Philip Morris R&D capability in developing new and improved smoking products."[438]

Some of Philip Morris' research attempted to assess the pharmacological effects of nicotine on youths. One study on the hyperkinetic child as prospective smoker observed that "amphetamines, which are strong stimulants, have the anomalous effect of quieting these children down"; the Philip Morris researchers initiated a study to determine "whether such children may not eventually become cigarette smokers in their teenage years as they discover *the advantage of self-stimulation via nicotine*."[439] This study was apparently

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[436] *Id.*

[437] *Id.* at 51-52, 57-94.

[438] Dunn WL, *Plans and Objectives–1979* (Dec. 6, 1978), in 141 Cong. Rec. H7669. *See* AR (Vol. 14 Ref. 175a).

[439] Ryan FJ (Philip Morris Inc.), Relationship between smoking and personality, in *Smoker Psychology/May 1-31, 1974* (Jun. 10, 1974), in 141 Cong. Rec. H7651 (daily ed. Jul. 25, 1995) (emphasis added). *See* AR (Vol. 14 Ref. 175a).

For a further description of Philip Morris' research into hyperkinetic children, *see* the following documents reprinted in 141 Cong. Rec. H7651-7657 (daily ed. Jul. 25, 1995):

> Ryan FJ (Philip Morris Inc.), Relationship between smoking and personality, in *Smoker Psychology/May 1-31, 1974* (Jun. 10, 1974). *See* AR (Vol. 14 Ref. 175a).

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never completed because "[o]bstacles presented by school systems and physicians . . . have made it very difficult for us to conduct studies using school and medical records of minors."[440] Another study initiated by Philip Morris involved administering "painful" electric shocks to college students to determine the anxiety-reducing effects of cigarettes.[441] Although preliminary findings supported the hypothesis that students with a high anxiety factor on personality tests would puff more frequently,[442] the study apparently had to be discontinued because "fear of shock is scaring away some of our more valuable

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Ryan FJ (Philip Morris Inc.), Hyperkinesis as a precursor of smoking, in *Smoker Psychology/Feb. 1-28, 1975* (Mar. 10, 1975). *See* AR (Vol. 14 Ref. 175a).

Philip Morris Research Center, *Behavioral Research Annual Report* (Jul. 18, 1975) (approved by Dunn WL). *See* AR (Vol. 14 Ref. 175a).

Ryan FJ (Philip Morris Inc.), Hyperactivity, in *Smoker Psychology/Apr. 1-30, 1977* (May 13, 1977). *See* AR (Vol. 14 Ref. 175a).

Ryan FJ (Philip Morris Inc.), Hyperkinetic children, in *Smoker Psychology/Feb. 1-28, 1978* (Mar. 10, 1978). *See* AR (Vol. 14 Ref. 175a).

[440] Ryan FJ (Philip Morris Inc.), Hyperkinetic children, in *Smoker Psychology/Feb. 1-28, 1978* (Mar. 10, 1978), in 141 Cong. Rec. H7657 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[441] Ryan FJ (Philip Morris Inc.), *Proposed Research Project: Smoking and Anxiety* (Dec. 23, 1969), in 141 Cong. Rec. H7648 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

For a further description of Philip Morris' research involving the administration of electric shocks, *see* the following documents printed in 141 Cong. Rec. H7648-7649 (daily ed. Jul. 25, 1995):

Ryan FJ (Philip Morris Inc.), Shock I, II, III, and IV, in *Consumer Psychology* (Sep. 16 - Oct.15, 1971). *See* AR (Vol. 14 Ref. 175a).

Ryan FJ (Philip Morris Inc.), Shock V, in *Consumer Psychology* (Jan. 15 - Feb. 15, 1972). *See* AR (Vol. 14 Ref. 175a).

Dunn WL (Philip Morris Inc.), *Quarterly Report-Projects 1600 and 2302* (Oct. 5, 1972). *See* AR (Vol. 14 Ref. 175a).

[442] Ryan FJ (Philip Morris Inc.), Shock I, II, III, and IV, in *Consumer Psychology Monthly Report* (Sep. 16 - Oct. 15, 1971), in 141 Cong. Rec. H7648-7649 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

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subjects."[443] In another study, Philip Morris proposed injecting nicotine into human subjects in order "to yield a broader picture of the role of the spike, the level, and the reinforcement characteristics of the substance."[444]

In congressional testimony, the former Philip Morris president, William Campbell, testified that to the extent that Philip Morris controls nicotine levels in cigarettes through blending, this is done "for taste."[445] Philip Morris's research program does not support this statement, however. The internal research documents in the administrative record show that Philip Morris exhaustively investigated the pharmacological properties of nicotine—not its gustatory properties. The intensive focus on nicotine pharmacology reflected in the documents indicates that Philip Morris regarded nicotine's contribution to cigarettes as pharmacological, not taste-related. Moreover, in its comments Philip Morris did not provide evidence of internal Philip Morris research into the taste characteristics of nicotine.

[443] Eichorn PA, Dunn WL (Philip Morris Inc.), *Quarterly Reports–Projects 1600 and 2302* (Oct. 5, 1972), in 141 Cong. Rec. H7649 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[444] Dunn WL (Philip Morris Inc.), *Plans and Objectives–1981* (Nov. 26, 1980), in 141 Cong. Rec. H7682 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

For a further description of Philip Morris' proposed research involving nicotine injections, *see*:

> Dunn WL (Philip Morris Inc.), *Behavioral Research Accomplishments, 1977* (Dec. 19, 1977), in 141 Cong. Rec. H7666 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).
>
> Dunn WL (Philip Morris Inc.), *Plans and Objectives–1979* (Dec. 6, 1978), in 141 Cong. Rec. H7669 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[445] *Regulation of Tobacco Products (Part 1): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 764 (Apr. 14, 1994) (testimony of William Campbell). *See* AR (Vol. 707 Ref. 1).

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Further examples of Philip Morris' research on nicotine pharmacology are presented in the Jurisdictional Analysis. *See* 60 FR 41590–41591, 41595–41599. Taken together, these studies show that Philip Morris conducted an extensive, sustained, and sophisticated investigation into the pharmacological effects of nicotine that gave the company knowledge that nicotine has significant pharmacological effects on smokers, including reinforcing effects. The research was conducted because of its commercial significance to Philip Morris; used techniques that are employed by government agencies to identify the "abuse potential" of drugs; and found that nicotine has hallmark characteristics of an addictive drug, including reinforcing effects and the development of tolerance.

iii. Project Table. Philip Morris' recognition of the important pharmacological role of nicotine in cigarettes has been consistent for over three decades. New evidence received by the Agency during the comment period, for instance, indicates that officials inside Philip Morris continued to recognize the importance of nicotine's pharmacological effects and uses in the 1990's.

A draft Philip Morris report on "Project Table," a proposal to develop "a nicotine delivery device" that relies on "heating rather than burning the tobacco" to "produce[] a cleaner, safer smoking experience," written around 1992, acknowledges that although "[d]ifferent people smoke for different reasons. . . . *the primary reason is to deliver nicotine into their bodies.*"[446] The report describes nicotine in cigarettes in explicit drug-like terms:

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[446] Philip Morris, Inc., Draft Report Regarding a Proposal for a "Safer" Cigarette, Code-named *Table*, at 1.5 (emphasis added). *See* AR (Vol. 531 Ref. 122).

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> Nicotine . . . is a physiologically active, nitrogen containing substance. *Similar organic chemicals include . . . quinine, cocaine, atropine and morphine*. While each of these substances can be used to affect human physiology, nicotine has a particularly broad range of influence.[447]

Project Table provides a detailed description of the pharmacological action of nicotine on the brain:

> *During the smoking act, nicotine is inhaled into the lungs in smoke, enters the bloodstream and travels to the brain in about eight to ten seconds.* The nicotine alters the state of the smoker by becoming a neurotransmitter and a stimulant. *Nicotine mimics the body's most important neurotransmitter, acetycholine (ACH), which controls heart rate and message sending within the brain. The nicotine is used to change physiological states leading to enhanced mental performance and relaxation.* A little nicotine seems to stimulate, while a lot sedates a person.[448]

The report also expressly places cigarettes and smokeless tobacco products in the same category of "nicotine delivery devices" that includes nicotine patches and inhalers, stating that "nicotine delivery devices range from snuff, chewing tobacco, cigars, pipes and conventional cigarettes to unique smoking articles, chewing gum, patches, aerosol sprays and inhalers."[449] The report thus indicates that the views of Philip Morris on the role of nicotine in cigarettes have been remarkably consistent. Twenty years after senior Philip Morris scientist William Dunn called cigarettes "a dispenser for a dose unit of nicotine,"[450] Philip Morris officials continue to regard nicotine as a drug and cigarettes as a "nicotine delivery device." The evidence of Philip Morris' statements and research on

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[447] *Id.* at 1 (emphasis added).

[448] *Id.* (emphasis added).

[449] *Id.* at 2.

[450] Dunn WL (Philip Morris Inc.), *Motives and Incentives in Cigarette Smoking* (1972), at 5. *See* AR (Vol. 12 Ref. 133).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

nicotine pharmacology persuasively documents that its cigarettes are intended to affect the structure or function of the body.

b. The Statements and Research of R. J. Reynolds

R.J. Reynolds Tobacco Company (RJR) is the nation's second largest cigarette manufacturer. The information in the administrative record shows that researchers and senior officials at RJR hold views on the pharmacological effects and uses of nicotine in cigarettes that are similar to those of the researchers and senior officials at Philip Morris.

i. The Teague Memoranda. During the comment period, FDA received two documents written by Claude Teague in 1972 and 1973, when he was the assistant director of research at RJR. Teague was subsequently promoted to director of corporate research in 1978.[451] These internal memoranda show that RJR scientists regarded nicotine as a "potent" and "habit-forming" drug; considered cigarettes to be "a vehicle for delivery of nicotine"; and conceived of the tobacco industry itself as "a specialized, highly ritualized and stylized segment of the pharmaceutical industry."

Teague's 1972 memorandum, entitled "Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of Nicotine Therein," makes four significant points. First, the memorandum describes nicotine as a powerful and habituating drug. According to the memorandum, nicotine is "a potent drug with a variety of physiological effects."[452] It is also "*known to be a habit-forming alkaloid.*"[453] Nicotine's specific effects on the body are described as follows:

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[451] *American Men and Women of Science, 1995-1996*, 19th ed. (New Providence: R.R. Bowker, 1995), 7:62. *See* AR (Vol. 711 Ref. 13).

[452] Teague CE. (R.J. Reynolds Tobacco Co.), *Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of Nicotine Therein* (Apr. 14, 1972), at 1. *See* AR (Vol. 531 Ref. 125).

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> The habituated user of tobacco products is said to derive "satisfaction" from nicotine. Although much studied, the physiological actions of nicotine are still poorly understood and appear to be many and varied. For example, . . . *at different dose levels, nicotine appears to act as a stimulant, depressant, tranquilizer, psychic energizer, appetite reducer, anti-fatigue agent, or energizer*, to name but a few of the varied and often contradictory effects attributed to it."[454]

Second, the memorandum acknowledges that nicotine is the "primary" reason for smoking. According to the memorandum:

> *[T]he confirmed user of tobacco products is primarily seeking the physiological "satisfaction" derived from nicotine*—and perhaps other active compounds. *His choice of product and pattern of usage are primarily determined by his individual nicotine dosage requirements. . . .*[455]

Third, the Teague memorandum describes cigarettes as drug delivery systems. According to the memorandum, "*a tobacco product is, in essence, a vehicle for delivery of nicotine*, designed to deliver the nicotine in a generally acceptable and attractive form."[456] The memorandum further states:

> If what we have said about the habituated smoker is true, then products designed for him should emphasize nicotine, nicotine delivery efficiency, nicotine satisfaction, and the like. *What we should really make and sell would be the proper dosage form of nicotine with as many other built-in attractions and gratifications as possible*—that is, an efficient nicotine delivery system with satisfactory flavor, mildness, convenience, cost, etc. . . . *Would it not be better, in the long run, to identify in our minds and in the minds of our customers what we are really selling, i.e., nicotine satisfaction?*[457]

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[453] *Id.* (emphasis added).

[454] *Id.* at 1-2 (emphasis added).

[455] *Id.* at 1 (emphasis added).

[456] *Id.*

[457] *Id.* at 5 (emphasis added).

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Indeed, the memorandum describes the tobacco industry itself as a "segment of the pharmaceutical industry":[458]

> In a sense, *the tobacco industry may be thought of as being a specialized, highly ritualized and stylized segment of the pharmaceutical industry*. . . . Our Industry is then based upon design, manufacture and sale of attractive dosage forms of nicotine, and our Company's position in our Industry is determined by our ability to produce dosage forms of nicotine which have more overall value, tangible or intangible, to the consumer than those of our competitors.[459]

Finally, the memorandum recommends improvements in the delivery of nicotine to consumers. In the short term, the memorandum recommends reducing tar levels while maintaining nicotine levels in cigarettes:

> Our critics have lumped "tar" and nicotine together in their allegations about health hazards. . . . *An accompanying Research Planning Memorandum suggests an approach to reducing the amount of "tar" in cigarette smoke per unit of nicotine*. That is probably the most realistic approach in today's market for conventional cigarette products.[460]

In the long term, the memorandum recommends a "more futuristic approach":[461]

> *If our business is fundamentally that of supplying nicotine in useful dosage form, why is it really necessary that allegedly harmful "tar" accompany that nicotine*? There should be some simpler, "cleaner", more efficient and direct way to provide the desired nicotine dosage than the present system involving combustion of tobacco or even chewing of tobacco. . . . It should be possible to obtain pure nicotine by synthesis or from high-nicotine tobacco. *It should then be possible, using modifications of techniques developed by the pharmaceutical and other*

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[458] *Id.* at 2.

[459] *Id.* (emphasis added).

[460] *Id.* at 6 (emphasis added).

[461] *Id.*

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> *industries, to deliver that nicotine to the user in efficient, effective, attractive dosage form, accompanied by no "tar", gas phase, or other allegedly harmful substances.* The dosage form could incorporate various flavorants, enhancers, and like desirable additives, and would *be designed to deliver the minimum effective amount of nicotine at the desired release-rate to supply the "satisfaction" desired by the user.* Such a product would maximize the benefits derived from nicotine, minimize allegedly undesirable over-dosage side effects from nicotine, and eliminate exposure to other materials alleged to be harmful to the user.[462]

Evidence in the record indicates that RJR acted on both of these recommendations. *See* sections II.C.2.b.iii. and II.C.3.b., below.

Claude Teague's 1973 memorandum, entitled "Some Thoughts about New Brands of Cigarettes for the Youth Market," recommends that RJR develop "new brands tailored to the youth market."[463] According to the memorandum, one of the design features that should be tailored to the youth market is nicotine delivery. The memorandum reaffirms that the "nicotine effects" and the other physical effects of smoking are "highly desirable to the confirmed smoker."[464] For the "pre-smoker" or "learner," however, the memorandum states that the physical effects of smoking, including the effects of nicotine, are "largely unknown, unneeded, or actually quite unpleasant or awkward."[465] Consequently, the memorandum recommends that "the effort here should be to affect a compromise to minimize the undesirable effects while retaining these which later become

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[462] *Id.* at 7 (emphasis added).

[463] Teague CE (R.J. Reynolds Tobacco Co.), *Research Planning Memorandum on Some Thoughts about New Brands of Cigarettes for the Youth Market* (Feb. 2, 1973), at 1. *See* AR (Vol. 531 Ref. 125).

[464] *Id.* at 4.

[465] *Id.* at 2, 4.

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desirable."[466] With respect to nicotine, the memorandum recommends that "nicotine should be delivered at about 1.0-1.3 mg/cigarette, the minimum for confirmed smokers. The rate of absorption of nicotine should be kept low by holding pH down, probably below 6."[467]

Teague's analysis shows that, as at Philip Morris, scientists at RJR have long understood that nicotine has significant pharmacological effects on the body and is the "primary" reason people smoke. His analysis further shows that, like Philip Morris scientists, RJR scientists also expressly conceived of cigarettes as a drug delivery system.

ii. Other Statements and Research of RJR Scientists and Officials. The views in the Teague memoranda about the "crucial role" of the pharmacological effects of nicotine continued to be expressed within RJR in later years. In approximately 1977, for instance, RJR researchers told the RJR marketing department that "*[w]ithout any question, the desire to smoke is based on the effect of nicotine on the body*";[468] that "*a confirmed smoker attempts to get a certain desired level of nicotine*";[469] and that "[t]he nicotine in the blood acts upon the central nervous system and produces in the average smoker a sensation one could describe as either stimulating or relaxing."[470] According to the RJR researchers, while nicotine has a role in "mouth taste" and "mouth satisfaction,"

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[466] *Id.* at 4.

[467] *Id.*

[468] Senkus M (R. J. Reynolds Tobacco Co.), *Some Effects of Smoking* (1976/1977), at 4 (emphasis added). *See* AR (Vol. 700 Ref. 593).

[469] *Id.* at 5 (emphasis added).

[470] *Id.* at 3.

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that is not nicotine's primary role; rather, "the ultimate satisfaction comes from the nicotine which is extracted . . . *in the lungs.*"[471]

In the late 1980's and early 1990's, moreover, RJR researchers conducted a series of experiments on how nicotine affects the brain. The published reports from these experiments revealed that 20 years after the Teague memoranda, RJR researchers continued to believe that: (1) nicotine has pharmacological effects on the brain; and (2) smokers smoke cigarettes primarily to obtain these pharmacological effects.

In a 1989 report entitled "Effects of Smoking/Nicotine on Anxiety, Heart Rate, and Lateralization of EEG During a Stressful Movie," RJR used an EEG to test its hypothesis that "nicotine and smoking help smokers to relax and cope with stress and negative affect" through "activation-reducing effects on the EEG."[472] The experiment's results supported RJR's hypothesis, indicating that nicotine produced the expected "anxiolytic" or anxiety-reducing effects in the brain:

> The present results support the view that the electrocortical effects of smoking are a function of environmental stress level, cigarette nicotine delivery, and cortical site. *They are also consistent with previous evidence that nicotine reduces anxiety and with our hypothesis that nicotine's anxiolytic properties are mediated by the right hemisphere.* Normal/high-nicotine delivery cigarettes, relative to low-nicotine control cigarettes, produced cortical activation (decreased alpha power) in both hemispheres during the no-stress control condition . . . but produced the opposite effect, decreased activation (increased alpha power), at the right parietal site during the three stressful movie scenes.[473]

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[471] *Id.* at 7-9 (emphasis added).

[472] Gilbert DG, Robinson JH, Chamberlin CL (R.J. Reynolds Tobacco Co.), *et al.*, Effects of smoking/nicotine on anxiety, heart rate, and lateralization of EEG during a stressful movie. *Psychophysiology* 1989;26(3):311-319, at 311. *See* AR (Vol. 14 Ref. 174-2).

[473] *Id.* at 316 (citation omitted) (emphasis added).

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The 1989 study used the EEG to measure smokers' brain waves while they watched a film containing graphic images of industrial accidents. In a 1991 study entitled "Electroencephalographic Effects of Cigarette Smoking," RJR researchers measured the effects of smoking on brain waves under "levels of mental workload representative of those encountered in day-to-day living."[474] They found that the pharmacological effects of smoking are affected by how deeply the smoker inhaled. According to the report:

> In light inhaling smokers, . . . smoking was found to attenuate EEG activity in the delta, theta, and alpha frequency bands . . . . In deep inhaling smokers, smoking produced a symmetrical central midline increase in beta2 magnitude, *an EEG effect that . . . is associated with anxiety relief.*[475]

These results led the RJR researchers to propose that light inhalers and deep inhalers smoke to obtain different pharmacological effects from nicotine and that the effects produced in deep-inhalers were comparable to the effects of benzodiazepines, a class of addictive drugs used for anxiety relief. According to the report:

> The results of the present investigation indicate that *light inhaling . . . smokers may smoke primarily for purposes of mental activation and performance enhancement.* This does not appear to be the case for deeper inhaling . . . smokers. . . . An extensive literature suggests that increased beta2 activity may reflect the anxiolytic properties of the benzodiazepines independently of sedative effects. *Thus, an important smoking motive for deep inhaling smokers might be anxiety reduction.*[476]

A year later, the RJR researchers reported the results of a study designed to isolate the precise effects of nicotine on the brain. In this study, some smokers were given

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[474] Pritchard WS (R.J. Reynolds Tobacco Co.), Electroencephalographic effects of cigarette smoking. *Psychopharmacology* 1991;104:485-490. at 486. *See* AR (Vol. 3 Ref. 23-2).

[475] *Id.* at 485 (emphasis added).

[476] *Id.* at 488 (citations omitted) (emphasis added).

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regular "light" cigarettes to smoke while others were given experimental cigarettes with virtually no nicotine. The results from the EEG showed that the regular "light" cigarette produced "a significant increase in beta2 magnitude," an effect associated with anxiety relief, and "a significant decrease in delta magnitude," an effect associated with improved mental alertness.[477] According to the researchers, "*this indicates that the beneficial effects of smoking on cognitive performance . . . are a function of nicotine absorbed from cigarette smoke upon inhalation.*"[478]

In another report written in 1992, the RJR researchers addressed the question "why do people smoke?" The researchers reject the claim that people smoke to satisfy an addiction, but they do not reject the claim that people smoke to obtain other pharmacological effects from nicotine. To the contrary, as Claude Teague did 20 years earlier, they assert that the reason people smoke is precisely to obtain these pharmacological effects:

> We believe that a more reasonable hypothesis concerning why people smoke . . . is that *smokers use cigarettes primarily as a 'tool' or 'resource' that provides them with needed psychological benefits (increased mental alertness, anxiety reduction, coping with stress).*[479]

In its comments, RJR asserts that nicotine is important in cigarettes because "nicotine plays an important role in the taste and flavor of cigarette smoke."[480] The

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[477] Robinson JH, Pritchard WS, Davis RA (R.J. Reynolds Tobacco Co.), Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine. *Psychopharmacology* 1992;108:466-472, at 469. *See* AR (Vol. 11 Ref. 129-3).

[478] *Id.* at 471 (emphasis added).

[479] Robinson J, Pritchard W (R.J. Reynolds Tobacco Co.). The role of nicotine in tobacco use. *Psychopharmacology* 1992;108:397-407, at 398 (emphasis added). *See* AR (Vol. 34 Ref. 589).

[480] R.J. Reynolds Tobacco Co., Comment (Jan. 2, 1996), at 50. *See* AR (Vol. 519 Ref. 103).

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history of RJR's research does not support the company's public position, however. If nicotine were important because of its role in taste, FDA would expect to find that RJR's research would focus on nicotine's impact on taste. The administrative record, however, contains virtually no RJR research demonstrating or investigating nicotine's influence on taste.[481] In contrast, RJR has extensively investigated the pharmacological impacts of nicotine. In total, the administrative record before FDA contains more than 20 studies published or funded by RJR on the effects of nicotine on the body.[482] The actual number

[481] There is little scientific support for the proposition that nicotine has an important role in cigarette taste. The four studies cited by RJR are all discussed in section II.B.2.c, above. Only one of the studies relied upon by RJR was actually conducted by RJR. This limited investigation by RJR into nicotine's role in taste was presented *after FDA's investigation had commenced.* Pritchard, WS, Robinson, JH, *The Sensory Role of Nicotine in Cigarette "Taste," Smoking Satisfaction and Desire to Smoke*, presented at the International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II (Montreal: Jul. 21-24, 1994). *See* AR (Vol. 519 Ref. 103, vol. II). As discussed in section II.B.2.c., above, RJR researchers conceded that the study was unable to distinguish the importance of any sensory aspects of nicotine from its pharmacological effects.

[482] Bjercke RJ, Langone JJ. Anti-idiotypic antibody probes of neuronal nicotinic receptors, *Biochem Biophys Res Commun* 1989;162(3):1085-1092. *See* AR (Vol. 46 Ref. 53).

Brazell MP, Mitchell SN, Gray JA. Effect of acute administration of nicotine on in vivo release of noradrenaline in the hippocampus of freely moving rats: a dose-response and antagonist study, *Neuropharmacology* 1991;30(8):823-833. *See* AR (Vol. 46 Ref. 58).

Byrd GD, Chang KM, Greene JM, *et al.*, Evidence for urinary excretion of glucuronide conjugates of nicotine, cotinine, and trans-3'-hydroxycotinine in smokers, *Drug Metab Dispos Biol Fate Chem* 1992;20(2):192-197. *See* AR (Vol. 120 Ref. 1131).

Caldwell WS, Green JM, Byrd GD, *et al.*, Characterization of the glucuronide conjugate of cotinine: a previously unidentified major metabolite of nicotine in smokers' urine, *Chem Res Toxicol* 1992;5(2):280-285. *See* AR (Vol. 46 Ref. 62).

Caldwell WS, Greene JM, Dobson GP, *et al.*, Intragastric nitrosation of nicotine is not a significant contributor to nitrosamine exposure, *Ann NY Acad Sci* 1993;686:213-227. *See* AR (Vol. 128 Ref. 1388).

Collins AC, Bhat RV, Pauly JR, *et al.*, Modulation of nicotine receptors by chronic exposure to nicotinic agonists and antagonists, in *The Biology of Nicotine Dependence*, eds. Bock G, Marsh J (CIBA Foundation Symposium 152, 1990), at 68-82. *See* AR (Vol. 47 Ref. 71).

deBethizy JD, Borgerding MF, Doolittle DJ, Chemical and biological studies of a cigarette that heats rather than burns tobacco, *J Clin Pharmacol* 1990;30(8):755-763. *See* AR (Vol. 47 Ref. 78).

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deBethizy JD, Robinson JH, Davis RA, *et al.*, Absorption of nicotine from a cigarette that does not burn tobacco, *Pharmacology* 1988;37(5):328-332. *See* AR (Vol. 47 Ref. 79).

Gilbert DG, Robinson JH, Chamberlin CL, *et al.*, Effects of smoking/nicotine on anxiety, heart rate, and lateralization of EEG during a stressful movie, *Psychophysiology* 1989;26(3):311-319. *See* AR (Vol. 14 Ref. 174-2).

Hammond DK, Bjercke RJ, Langone JJ, *et al.*, Metabolism of nicotine by rat liver cytochromes P-450, Assessment utilizing monoclonal antibodies to nicotine and cotinine, *Drug Metab Dispos Biol Fate Chem* 1991;19(4):804-808. *See* AR (Vol. 48 Ref. 110).

Kyerematen GA, Morgan ML, Chattopadhyay B, *et al.*, Disposition of nicotine and eight metabolites in smokers and nonsmokers, *Clin Pharmacol Ther* 1990;48(6):641-651. *See* AR (Vol. 49 Ref. 146).

Kyerematen GA, Taylor LH, deBethizy JD, *et al.*, Pharmacokinetics of nicotine and 12 metabolites in the rat, Application of a new radiometric high performance liquid chromatography assay, *Drug Metab Dispos Biol Fate Chem* 1988;16(1):125-129. *See* AR (Vol. 49 Ref. 145).

Lippiello PM, Fernandes KG, The binding of L-[3H]nicotine to a single class of high affinity sites in rat brain membranes, *Mol Pharmacol* 1986;29(5):448-454. *See* AR (Vol. 55 Ref. 165).

Lippiello PM, Mencherif M, Prince RJ, The role of desensitization in CNS nicotinic receptor function, in *International Symposium on Nicotine: The Effects of Nicotine on Biological Systems* 1994, S11. *See* AR (Vol. 55 Ref. 166).

Lippiello PM, Sears SB, Fernandes KG, Kinetics and mechanism of L-[3H]nicotine binding to putative high affinity receptor sites in rat brain, *Mol Pharmacol* 1987;31(4):392-400. *See* AR (Vol. 55 Ref. 162).

Marks MJ, Grady SR, Collins AC, Downregulation of nicotinic receptor function after chronic nicotine infusion, *J Pharmacol Exp Ther* 1993;266(3):1268-1276. *See* AR (Vol. 55 Ref. 176).

Mitchell SN, Brazell MP, Joseph MH, *et al.*, Regionally specific effects of acute and chronic nicotine on rates of catecholamine and 5-hydroxytryptamine synthesis in rat brain, *Eur J Pharmacol* 1989;167(3):311-322. *See* AR (Vol. 57 Ref. 200).

Mitchell SN, Brazell MP, Schugens MM, *et al.*, Nicotine-induced catecholamine synthesis after lesions to the dorsal or ventral noradrenergic bundle, *European Journal of Pharmacology* 1990;179(3):383-391. *See* AR (Vol. 57 Ref. 197).

Pritchard WS, Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490. *See* AR (Vol. 3 Ref. 23-2).

Pritchard WS, Gilbert DG, Duke DW, Flexible effects of quantified cigarette smoke delivery on EEG dimensional complexity, *Psychopharmacology* 1993;113:95-102. *See* AR (Vol. 3 Ref. 23-1).

Pritchard WS, Robinson JH, Guy TD, Enhancement of continuous performance task reaction time by smoking in non-deprived smokers, *Psychopharmacology* 1992;108:437-442. *See* AR (Vol. 67 Ref. 72).

Robinson JH, Pritchard WS, Davis RA, Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine, *Psychopharmacology* 1992;108:466-472. *See* AR (Vol. 59 Ref. 236).

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of RJR studies may be much higher. According to an RJR spokesperson, "[w]e've not only done research on the pharmacological effects of nicotine but we've published it in at least 250 peer-reviewed journals and symposia."[483]

RJR's sustained and sophisticated research into nicotine pharmacology demonstrates that RJR knows that (1) its product will affect consumers in a drug-like manner and (2) consumers will use its product to obtain these drug effects.

iii. RJR's Alternative Tobacco Products. Further evidence of RJR's understanding of the central role of nicotine in smoking is provided by RJR's development of alternative tobacco products that are designed to deliver nicotine, but not other constituents of cigarette smoke, to the consumer.

RJR's efforts to develop alternative nicotine delivery systems began more than 20 years ago. As noted above, Claude Teague recommended in 1972 that RJR develop "some simpler, 'cleaner', more efficient and direct way to *provide the desired nicotine dosage* than the present system involving combustion of tobacco."[484] In recent years, RJR has developed at least two alternative tobacco products.

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Smith KM, Mitchell SN, Joseph MH, Effects of chronic and subchronic nicotine on tyrosine hydroxylase activity in noradrenergic and dopaminergic neurones in the rat brain. *J Neurochem* 1991;57(5):1750-1756. *See* AR (Vol. 60 Ref. 266).

Wonnacott S, Drasdo AL. Presynaptic actions of nicotine in the CNS, in *Effects of Nicotine on Biological Systems*, eds. Adlkofer F, Thurau K (1991), at 295-305. *See* AR (Vol. 62 Ref. 302).

[483] Collins G, Legal attack on tobacco intensifies, *New York Times*, Jun. 9, 1995. *See* AR (Vol. 21 Ref. 240a).

[484] Teague CE (R.J. Reynolds Tobacco Co.), *Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of Nicotine Therein* (Apr. 14, 1972), at 7 (emphasis added). *See* AR (Vol. 531 Ref. 125).

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II.C.2.

First, in the late 1980's, RJR developed and briefly marketed Premier, a product that worked by heating nicotine and glycerol-coated aluminum beads contained in an aluminum cylinder rather than by burning tobacco. Premier resembled a conventional cigarette in appearance only. Inside, it contained a carbon tip, which served as the heat source for the aluminum cylinder.[485] RJR documents show that RJR was acutely interested in Premier's ability to deliver nicotine to the smoker's blood and brain. For instance, RJR conducted extensive plasma studies to show that smokers using Premier would achieve approximately the same level of nicotine in their blood as smokers using conventional cigarettes.[486] Other smoke components, however, were reduced by about 90%.[487] Premier functioned like the alternative nicotine delivery system recommended by Teague. Indeed, RJR used Teague's terminology to market Premier, advertising the product as a "cleaner" cigarette.[488]

More recently, RJR has begun test-marketing a low-smoke product called Eclipse.[489] Like Premier, Eclipse relies on a carbon tip as a heat source. The tip heats a

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[485] *Chemical and Biological Studies on New Cigarette Prototypes that Heat Instead of Burn Tobacco* (Winston-Salem NC: R.J. Reynolds Tobacco Co., 1988), at 1-10. *See* AR (Vol. 107 Ref. 980).

[486] *Id.* at vii, 457-458, 479-483, 490-492.

deBethizy JD, Borgerding MF, Doolittle DJ, *et al.* (R.J. Reynolds), Chemical and Biological Studies of a Cigarette that Heats Rather than Burns Tobacco, *J. Clin. Pharmacol.*, 1990;30:755-763. *See* AR (Vol. 47 Ref. 78).

[487] *Id.* at 757.

[488] Pollay RW, Carter-Whitney D, *More Chronological Notes on the Promotion of Cigarettes* (History of Advertising Archives, Aug. 1990), at 29. *See* AR (Vol. 215 Ref. 2891).

[489] Cabell B, Smokeless cigarette makers hope to Eclipse market, Live Report (Jun. 3, 1996). *See* AR (Vol. 711 Ref. 11).

Jones C, Reynolds not blowing smoke when it comes to keeping a lid on Eclipse, *The Richmond Times Dispatch* (Jun. 10, 1996). *See* AR (Vol. 711 Ref. 12).

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glycerin supply in the cigarette rod, which vaporizes and extracts nicotine, but is intended to produce very little of the normal constituents of tar, as it passes through the rod to the smoker's mouth. The final Eclipse smoke vapor is 85% water, glycerol, and nicotine (versus 25% in standard cigarette smoke) and only 15% tar (versus 75% in standard smoke).[490] Thus, Eclipse is intended to deliver nicotine at levels similar to conventional ultra-low-tar cigarettes, but much lower levels of tar.[491]

In its comments, RJR asserts that "Premier *was* a cigarette" because it provided the smoker with "smoking taste and pleasure."[492] Likewise, RJR asserts that "Eclipse is a cigarette."[493] But the major similarity in the vapor from Premier and Eclipse and the smoke from a conventional cigarette is the nicotine delivery. The implication of RJR's work on Premier and Eclipse is that nicotine delivery is the defining characteristic of a cigarette. As RJR informed FDA officials during the launch of Premier, "without nicotine, you don't have a cigarette."[494] Premier and Eclipse are thus evidence that conventional cigarettes are, in effect, simply nicotine delivery systems.

iv. RJR's Legal Briefs. Before the Agency, RJR argues that nicotine is not addictive and that the Agency should not believe the widespread "allegations" to the

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[490] Hilts P, Little smoke, but still lots of nicotine, *New York Times*, Nov. 27, 1994. See AR (Vol. 34 Ref. 568).

[491] Feder BJ, Ready to test new cigarette, maker fears tough rules, *New York Times*, Apr. 8, 1996. *See* AR (Vol. 700 Ref. 225).

[492] R.J. Reynolds Tobacco Co., Comment (Jan. 2, 1996), at 34-35 (emphasis added). *See* AR (Vol. 519 Ref. 103).

[493] R.J. Reynolds Tobacco Co., Comment (Apr. 19, 1996). *See* AR (Vol. 700 Ref. 225).

[494] Department of Health and Human Services, Memorandum of meeting, *RJR's "Smokeless" Cigarette* (Oct. 23, 1987), at 3. *See* AR (Vol. 34 Ref. 558-2).

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contrary. However, RJR has taken exactly the opposite position in court cases. There RJR argues that the risk of becoming addicted to cigarettes is so foreseeable to consumers that consumers must be held to have assumed the risk. For instance, in one case RJR argued that consumers should not be allowed to sue cigarette manufacturers on the grounds that they become addicted, because they should have foreseen this risk:

> There can be no serious suggestion that ordinary consumers do not expect to find nicotine in cigarettes, or that ordinary consumers have not long been well aware that it may be very difficult to stop smoking. *The common knowledge of the alleged habituating or "addicting" properties of cigarettes has resulted in almost casual references to these properties in decisions from around the country throughout this century.*[495]

RJR asserts that this statement does not acknowledge addiction because RJR is merely stating that "allegations" concerning the addictive properties of cigarettes are well known. However, RJR's position in the litigation and its position before the Agency are in fundamental conflict. RJR cannot consistently deny its awareness of nicotine's addictive properties while at the same time claiming that its consumers should be deemed to have an awareness of these properties. RJR's recognition of "the common knowledge of the alleged habituating or 'addicting' properties of cigarettes" is thus further evidence of RJR's awareness of the addictive and other pharmacological effects of cigarettes.

In sum, the internal RJR memoranda in the administrative record, RJR's published research into nicotine pharmacology, RJR's development of alternative tobacco products that function as nicotine delivery devices, and even RJR's litigation briefs all point to the

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[495] Appellees brief in reply to appellants' opposition to petition for transfer, *Rogers v. R.J. Reynolds et al.* (Sup. Ct. Ind.) (No. 49A02-8904 CV 164) (1990), at 7-8 (citation omitted) (emphasis added). *See* AR (Vol. 21 Ref. 229).

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conclusion that RJR knows that its cigarettes will have pharmacological effects, that consumers will purchase its products to obtain these effects, and that, in essence, its cigarettes function as nicotine delivery devices. This is persuasive evidence that RJR intends its product to affect the structure and function of the body.

c. The Statements and Research of Brown & Williamson

The administrative record includes a large array of documents from the Brown & Williamson Tobacco Corporation, the third largest cigarette manufacturer in the United States, and its corporate parent, BAT Industries PLC, formerly British-American Tobacco Company (BATCO). These documents show that Brown & Williamson and BATCO have conducted extensive research on nicotine's pharmacological effects and that for over 30 years senior researchers and officials at Brown & Williamson and BATCO have considered nicotine to be "addictive;"[496] "an extremely biologically active compound capable of eliciting a range of pharmacological, biochemical and physiological responses"[497] and the reason "why people inhale smoke."[498]

The documents from Brown & Williamson and BATCO in the administrative record include many unpublished reports from company research, internal memoranda, and reports from conferences of company scientists. These documents are summarized in the following chronology, which illustrates that the companies have long regarded

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[496] *See, e.g.*, Yeaman A (Brown & Williamson), *Implications of Battelle Hippo I and II and the Griffith Filter* (Jul. 17, 1963), at 4. *See* AR (Vol. 21 Ref. 221).

[497] BATCO Group R&D, *Method for Nicotine and Cotinine in Blood and Urine* (May 21, 1980), at 2. *See* AR (Vol. 23 Ref. 300-1).

[498] Greig CC (BATCO), *Short Lived Species in Smoke* (Jan. 26, 1984), attached to letter from Ayres CI (BATCO) to Kohnhorst EE (Brown & Williamson) (Feb. 9, 1984), at 10. *See* AR (Vol. 34 Ref. 584).

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themselves as "in a nicotine rather than a tobacco industry."[499] Although the statements of company scientists and officials seem to become somewhat more guarded with time, the documents show a consistent recognition of nicotine's pharmacological effects and uses, including its role in causing and sustaining addiction.

i. Statements and Research in the 1960's. In the 1960's, senior officials at BATCO and Brown & Williamson and their senior researchers candidly discussed nicotine's "addictive" and "drug" effects in internal meetings. In a 1962 conference of BATCO researchers, for instance, Charles Ellis, the science advisor to the BATCO board, acknowledged that "*smoking is a habit of addiction.*"[500] He described the role of nicotine in cigarettes as follows:

> *It is my conviction that nicotine is a very remarkable beneficent drug that both helps the body to resist external stress and also can as a result show a pronounced tranquillising effect. . . . Nicotine is not only a very fine drug, but the techniques of administration by smoking has [sic] considerable psychological advantages and a built-in control against excessive absorption.* It is almost impossible to take an overdose of nicotine in the way it is only too easy to do with sleeping pills.[501]

Charles Ellis recommended that BATCO conduct research "to investigate whether cigarette smoke produces effects on the central nervous system characteristic of tranquilising or stimulating drugs and, if so, to see if such activity is due solely to nicotine."[502] The Battelle Memorial Institute in Geneva, Switzerland, conducted this

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[499] Johnson RR (BATCO), *Comments on Nicotine* (Jun. 30, 1963), at 10-11. *See* AR (Vol. 21 Ref. 242).

[500] Ellis C (BATCO), *The smoking and health problem*, in *Smoking and Health--Policy on Research*, Research Conference, Southampton, England (1962), at 4 (emphasis added). *See* AR (Vol. 21 Ref. 220).

[501] *Id.* at 15-16 (emphasis added).

[502] *Id.* at 16.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

research for BATCO, producing a series of reports in 1963 called "HIPPO I," "HIPPO II," "The Fate of Nicotine in the Body," and "A Tentative Hypothesis on Nicotine Addiction."

These reports substantiated and explained nicotine's drug-like and addictive effects. "HIPPO II," for instance, suggested that "*the key to the explanation of both phenomena of tolerance and of addiction*" to nicotine could be found through "[a] quantitative investigation of the relations with time of nicotine—and of some possible brain mediators—on adreno-corticotrophic activity."[503] The report further stated that "the so-called 'beneficial effects' of nicotine are of two kinds: 1. Enhancing effect on the pituitary-adrenal response to stress; 2. Regulation of body weight."[504]

Similarly, "The Fate of Nicotine in the Body" found that nicotine "*appears to be intimately connected with the phenomena of tobacco habituation (tolerance) and/or addiction.*"[505] It also reported "[t]here is increasing evidence that *nicotine is the key factor in controlling, through the central nervous system, a number of beneficial effects of tobacco smoke*, including its action in the presence of stress situations."[506]

"A Tentative Hypothesis on Nicotine Addiction" stated that "the hypothalomo-pituitary stimulation of nicotine is *the beneficial mechanism which makes people smoke.*

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[503] Haselbach C, Libert O, *Final Report on Project HIPPO II* (Mar. 1963), at 4 (emphasis added). *See* AR (Vol. 64 Ref. 321).

[504] *Id.* at 2.

[505] Clemmesen H, Haselbach C, *The Fate of Nicotine in the Body* (May 1963), at 1 (emphasis added). *See* AR (Vol. 21 Ref. 243).

[506] *Id.* at 1 (emphasis added).

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in other words, nicotine helps people to cope with stress."[507] The report then suggested that nicotine addiction could be explained as follows:

> If nicotine intake, however, is prohibited to chronic smokers, the corticotropin-releasing ability of the hypothalmus is greatly reduced, so that these individuals are left with an unbalanced endocrine system. *A body left in this unbalanced status craves for renewed drug intake in order to restore the physiological equilibrium. This unconscious desire explains the addiction of the individual to nicotine.*[508]

The Battelle reports were distributed to the top officials at Brown & Williamson and other tobacco companies. Charles Ellis sent copies of the Battelle reports to the president of Brown & Williamson, William S. Cutchins. Brown & Williamson in turn sent the Project Hippo reports to RJR.[509]

In July 1963, Brown & Williamson's general counsel, Addison Yeaman, wrote an internal memorandum entitled "Implications of Battelle Hippo I and II and the Griffith Filter." He stated that "*nicotine is addictive*" and that "*[w]e are, then, in the business of selling nicotine, an addictive drug . . .* "[510]

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[507] Haselbach C, Libert O. *A Tentative Hypothesis on Nicotine Addiction* (May 30, 1963), at 1 (emphasis added). *See* AR (Vol. 20 Ref. 197).

[508] *Id.* at 2 (emphasis added).

[509] *Note to Cutchins WS (Brown & Williamson) (* Jun. 19, 1963). *See* AR (Vol. 14, Ref. 165-4).

Letter from Ellis C (BATCO) to Yeaman AY (Brown & Williamson) (Jun. 28, 1963). *See* AR (Vol. 14 Ref. 165-2).

Letter from Yeaman AY (Brown & Williamson) to Jacob EJ (R.J. Reynolds Co.) (Aug. 5, 1963). *See* AR (Vol. 14 Ref. 165-3).

[510] Yeaman AY (Brown & Williamson), *Implications of Battelle Hippo I and II and the Griffith Filter* (Jul. 17, 1963), at 4 (emphasis added). *See* AR (Vol. 21 Ref. 221).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

These views were frequently reiterated. In June of 1967, Charles Ellis stated, "*we are in a nicotine rather than a tobacco industry.*"[511] Several months later, at an October 1967 meeting, BATCO researchers agreed that "*[s]moking is an addictive habit attributable to nicotine.*"[512]

In 1968, Sidney J. Green, who was a member of BATCO's board as well as the company's director of research, acknowledged that one "recognisable type" of smoking behavior is "*addictive*" smoking. He added, "it seems a good assumption that *nicotine plays a predominant role for many smokers. . . . [A] good part of the tobacco industry is concerned with the administration of nicotine to consumers.*"[513]

Similarly, at another BATCO research conference in 1968, the researchers agreed that nicotine has "*pre-eminent importance*" and that "the pharmacology of nicotine should continue to be kept under review."[514]

A year later, at a 1969 meeting of BATCO researchers, BATCO scientist D. J. Wood stated:

> The presence of nicotine is the reason why the tobacco plant was singled out from all other plants for consumption in this rather unusual way.
>
> *Nicotine has well documented pharmacological action. It is claimed to have a dual effect, acting both as a stimulant and a tranquilliser. It is believed to be responsible for the "satisfaction"*

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[511] Johnson RR (BATCO), *Comments on Nicotine* (Jun. 30, 1963), at 10 (emphasis added). *See* AR (Vol. 21 Ref. 242).

[512] Minutes of BATCO Group R&D Conference at Montreal, Canada (Oct. 24, 1967), at 2 (emphasis added). *See* AR (Vol. 21 Ref. 206-4). FDA notes that the version of this document made public by Congress contains a handwritten edit changing "an addictive habit" to "a habit."

[513] Green SJ (BATCO), *BAT Group Research* (Sep. 4, 1968), at 1-2 (emphasis added). *See* AR (Vol. 15 Ref. 192).

[514] Minutes of BATCO Research Conference at Hilton Head, SC (Sep. 24-30, 1968), at 3 (emphasis added). *See* AR (Vol. 31 Ref. 525-1).

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of smoking, using this term in the physiological rather than the psychological sense.[515]

And at another 1969 conference of BATCO scientists, the following conclusion was reached: "*[t]he Conference agreed that all the evidence continues to demonstrate the importance of nicotine to the smoker. . . .*"[516]

Numerous other similar statements were made by Brown & Williamson and BATCO researchers and officials in the 1960's. They are described in the Jurisdictional Analysis. *See* 60 FR 41584–41586. Collectively, these statements show that even as early as the 1960's, Brown & Williamson and BATCO officials knew the addictive and other pharmacological effects of nicotine, knew that consumers smoked cigarettes for these effects, and viewed themselves as in the drug delivery business.

ii. Statements and Research in the 1970's and 1980's. Throughout the 1970's and 1980's, Brown & Williamson and BATCO officials continued to emphasize the importance of nicotine in cigarettes. At a 1970 conference of BATCO researchers, for instance, the researchers postulated that "*[n]icotine is important, and there is probably a minimum level necessary for consumer acceptance in any given market.*"[517]

In 1972, S.J. Green, the BATCO board member and research director, stated that "*[t]he tobacco smoking habit is reinforced or dependent upon the psycho-*

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[515] Wood DJ (BATCO), *Aspects of the R&DE Function*, Notes for a talk given by Wood DJ at Chelwood, Sep. 1969 (Jul. 20, 1970), at 7 (emphasis added). *See* AR (Vol. 22 Ref. 287).

[516] Minutes of BATCO Research Conference at Kronberg (Jun. 2-6, 1969), at 7 (emphasis added). *See* AR (Vol. 14 Ref. 172-4).

[517] Summary and conclusions of BAT Group Research Conference at St. Adele, Quebec (Nov. 9-13, 1970), at 1 (emphasis added). *See* AR (Vol. 23 Ref. 294).

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pharmacological effects mainly of nicotine."[518] Similarly, a 1972 BATCO research report observed:

> It has been suggested that *a considerable proportion of smokers depend on the pharmacological action of nicotine for their motivation to continue smoking.*
>
> If this view is correct, *the present scale of the tobacco industry is largely dependent on the intensity and nature of the pharmacological action of nicotine.*[519]

These statements demonstrate an awareness that nicotine has "reinforcing" effects, one of the hallmarks of an addictive substance, and that the tobacco industry is built upon these effects.

At a 1974 BATCO conference, company scientists reported that BATCO research had found that consumers appear to smoke to fulfill their "nicotine requirements," stating that "the Kippa study suggests that whatever the characteristics of cigarettes as determined by smoking machines, *the smoker adjusts his pattern to deliver his own nicotine requirements (about 0.8 mg per cigarette).*"[520]

At a 1976 BATCO conference on smoking behavior, the researchers again stated that nicotine has reinforcing effects on smokers, observing that nicotine is "*known to be pharmacologically active in the brain*" and is "*considered to be the reinforcing factor in the smoking habit for at least 80% of smokers.*"[521]

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[518] Green SJ (BATCO), *The Association of Smoking and Disease* (Jul. 26, 1972), at 1 (emphasis added). *See* AR (Vol. 15 Ref. 193).

[519] Kilburn KD, Underwood JG (BATCO), *Preparation and Properties of Nicotine Analogues* (Nov. 9, 1972), at 2 (citations omitted) (emphasis added). *See* AR (Vol. 31 Ref. 524-1).

[520] Notes on BATCO Group R&D Conference at Duck Key, FL (Jan. 12-18, 1974), at 2 (emphasis added). *See* AR (Vol. 25 Ref. 327).

[521] Minutes of BATCO Group R&D Conference on Smoking Behaviour at Southampton, England (Oct. 11-12, 1976), at BW-W2-02145, BW-W2-02152–BW-W2-02153 (emphasis added). *See* AR (Vol. 14 Ref. 180).

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II.C.2.

At a 1977 conference, nicotine was once more the "focal point." A Brown & Williamson summary of the conference stated that "[i]n many cases, psychological and physiological changes observed in subjects . . . were shown to be due to nicotine" and "[m]ost researchers conclude that *the nicotine effect is biphasic and dosage dependent: small doses stimulate and large doses depress.*"[522]

A year later, BATCO board member and chief researcher S.J. Green explicitly acknowledged that nicotine is addictive. Specifically, he wrote "*[t]he strong addiction to cigarette[s] removes freedom of choice from many individuals.*"[523]

A 1980 BATCO research report stated that "*[n]icotine is an extremely biologically active compound capable of eliciting a range of pharmacological, biochemical and physiological responses in vivo.*"[524]

A 1981 report on the pharmacology of nicotine by the Tobacco Advisory Council, which represents U.K. tobacco manufacturers including BATCO, stated that "*nicotine is regarded as the most pharmacologically-active compound in tobacco smoke*" and concluded that "*[i]n a nutshell, our approach has been to regard nicotine as a 'drug.*"[525]

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[522] Trip report of BATCO International Smoking Behavior Conference at Chelwood Vachery, England (Jan. 6, 1978), at 1-2 (emphasis added). *See* AR (Vol. 178 Ref. 2075).

[523] Notes of Green SJ (1978) (emphasis added). *See* AR (Vol. 528 Ref. 97, appendix 18).

[524] BATCO Group R&D, *Method for Nicotine and Cotinine in Blood and Urine* (May 21, 1980), at 2 (emphasis added). *See* AR (Vol. 23, Ref. 300-1).

[525] Cohen AJ, Roe FJC (Tobacco Advisory Council), *Monograph on the Pharmacology and Toxicology of Nicotine* (1981), at 1, 17 (emphasis added). *See* AR (Vol. 14 Ref 184).

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II.C.2.

In 1982, a market research report for Imperial Tobacco Ltd., BATCO's Canadian subsidiary, referred to attitudes of adolescents "[o]nce addiction does take place," and states that "addicted they do indeed become."[526] The report goes on:

> Recidivism has several causes . . . [including] the belief that after a few weeks off cigarettes, one could begin again to smoke 'just a few.' . . . This 'just a few' business is actually *a surrender to addiction* while trying to . . . *pretend to oneself and to others that addiction is no longer present, which is nonsense.*[527]

At a 1983 BATCO research conference, the minutes of the proceedings state that "*[t]he basic assumption is that nicotine . . . is almost certainly the key smoke component for satisfaction . . .*"[528]

In a 1984 letter, C. I. Ayres of BATCO wrote to E. E. Kohnhorst, the executive vice president and chief operating officer of Brown & Williamson, enclosing a report stating that nicotine is "why people inhale smoke":

> *It is well known that nicotine can be removed from smoke by the lung and transmitted to the brain within seconds of smoke inhalation.* Since it is the major or sole pharmacologically active agent in smoke, *it must be presumed that this is its preferred method of absorption and thus why people inhale smoke.*[529]

In 1984, BATCO also held two research conferences at which nicotine was extensively discussed. At the first conference, BATCO researchers held sessions on

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[526] Kwechansky Marketing Research (report prepared for Imperial Tobacco Ltd.), *Project Plus/Minus* (May 7, 1982), at i, 26 (emphasis added). *See* AR (Vol. 108 Ref. 1571).

[527] *Id.* at 36-37 (emphasis added).

[528] Minutes of BATCO Research Conference at Rio de Janeiro (Aug. 22-26, 1983), at 10 (emphasis added). *See* AR (Vol. 179 Ref. 2067).

[529] Greig CC, *Short Lived Species in Smoke* (Jan. 26, 1984), attached to letter from Ayres CI (BATCO) to Kohnhorst EE (Brown & Williamson) (Feb. 9, 1984), at 10 (emphasis added). *See* AR (Vol. 34 Ref. 584).

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"Nicotine Dose Requirement-Background," "Nicotine Dose Estimation," "Effects of Nicotine—Interaction with the Brain (Pharmacology)," and "Product Modification for Maximal Nicotine Effects."[530] The researchers reported that "*[i]ntuitively it is felt that 'satisfaction' must be related to nicotine. Many people believe it [is] a 'whole body response' and involves the action of nicotine in the brain.*"[531] They also acknowledged "*the central role of nicotine in the smoking process and our business generally.*"[532]

At the second conference, BATCO researchers reported that "*in its simplest sense puffing behaviour is the means of providing nicotine dose in a metered fashion.*"[533] According to one BATCO researcher speaking at the conference:

> Smoking is . . . a personal tool used by the smoker to refine his behaviour and reactions to the world at large.
>
> It is apparent that *nicotine largely underpins these contributions through its role as a generator of central physiological arousal effects* which express themselves as changes in human performance and psychological well-being."[534]

Other similar statements are summarized in the Jurisdictional Analysis. *See* 60 FR 41584-41666. Like the statements quoted above, they show that scientists at Brown &

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[530] Ayres CI (BATCO), Notes from the GR&DC [Group Research and Development Centre] Nicotine Conference at Southampton, England (Jul. 9-12, 1984) (slide), at BW-W2-02639. *See* AR (Vol. 14 Ref. 172).

[531] Minutes of BATCO Nicotine Conference at Southampton, England (Jun. 6-8, 1984), at BW-W2-01977 (emphasis added). *See* AR (Vol. 22 Ref. 287-6).

[532] Ayres CI (BATCO), Notes from the GR&DC [Group Research and Development Centre] Nicotine Conference at Southampton, England (Jul. 9-12, 1984), at 62 (emphasis added). *See* AR (Vol. 14 Ref. 172-1).

[533] Proceedings of BATCO Group R&D Smoking Behaviour-Marketing Conference, Session I (Jul. 9-12, 1984) (slide), at BW-W2-03242 (emphasis added). *See* AR (Vol. 21 Ref. 238).

[534] Harris RP, *The role of smoking behaviour in product development: some observations on the psychological aspects of smoking behaviour*, in Proceedings of BATCO Group R&D Smoking Behaviour-Marketing Conference, Session III (Jul. 9-12, 1984), at 79 (emphasis added). *See* AR (Vol. 192 Ref. 2172).

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Williamson and BATCO devoted extensive attention to understanding the pharmacological effects and uses of nicotine, consistently regarded nicotine as being the primary reason consumers smoked, and viewed cigarettes as nicotine delivery devices.

iii. Statements and Research in the 1990's. New documents received by FDA during the public comment period demonstrate that researchers and officials of Brown & Williamson and BATCO continue to hold similar views about nicotine in cigarettes in the 1990's. The new documents are a series of memoranda relating to the potential purchase in 1992 by BATCO of a manufacturer of nicotine patches, Stowic Resources Ltd.[535]

Brown & Williamson's research department evaluated the potential purchase in a memorandum entitled "Transdermal Nicotine Patches." Brown & Williamson researchers observed that "[t]here is currently a void in the market for a product that provides tobacco satisfaction in a form that is acceptable and available to many segments of the market" and recommended that "[w]e should be looking for opportunities to fill the void."[536] However, Brown & Williamson researchers expressed doubts that a nicotine patch could provide consumers with the same pharmacological effects obtained by smoking:

> The pattern of the blood nicotine concentrations attained by smoking vs the patch, however, are different. *With smoking, blood nicotine absorption is very rapid.* Blood nicotine concentrations go through a series of peaks and troughs with successive cigarette smoking throughout the day. . . . With the patch, nicotine absorption is relatively slow and continuous and peak blood levels are not as high as with cigarette smoking. *A major advantage of cigarette smoking over the nicotine patch system is the ability for*

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[535] Salter R, *Transdermal Nicotine* (Apr. 3, 1992); Research and Development, *Response to BAT Industries Note on Transdermal Nicotine (28.02.92)* (Mar. 27, 1992); Kausch, Research and Development/Quality, *Transdermal Nicotine*; Research and Development/Quality, *Transdermal Nicotine Patches*; McGraw M (Brown & Williamson), *Nicotine Delivery Systems* (Apr. 24, 1992). *See* AR (Vol. 531 Ref. 124).

[536] *Transdermal Nicotine Patches*, at 3. *See* AR (Vol. 531 Ref. 124).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

the smoker to have very flexible control over titrating his desired dose of nicotine.[537]

Similar views were expressed by other BAT Industries subsidiaries. BAT Industries' German subsidiary, for instance, stated that "*[t]he rapid, peaking intake of nicotine which the smoker clearly wants cannot be achieved with nicotine application via . . . plaster.*"[538]

The German subsidiary further acknowledged that nicotine can produce dependency and addiction. According to the German report, which was distributed by BAT Industries to the then president of Brown & Williamson, R. J. Pritchard, "*[t]he disadvantage of rapid nicotine intake similar to that achieved with a cigarette is seen in the danger of people possibly becoming dependent on it.*"[539] The German subsidiary observed that even with nicotine gum there is a "*danger of addiction,*" stating that "the smoker can organize intake to suit himself" and achieve "[a]ctive control over intake and the condition it produces."[540]

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Brown & Williamson's legal department argued against the purchase of Stowic on legal grounds, warning that it would suggest that Brown & Williamson is in "the nicotine delivery business" and cause Brown & Williamson to "*run a serious risk of facing FDA jurisdiction.*" The lawyers also argued that the purchase of Stowic would have "disastrous" implications for product liability litigation because "*[t]he marketing of any*

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[537] *Id.* at 2 (emphasis added).

[538] Research and Development/Quality, *Re: Transdermal Nicotine*, at 3 (emphasis added). *See* AR (Vol. 531 Ref. 124).

[539] *Id.* at 3 (emphasis added).

[540] *Id.* at 2.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

nicotine delivery system undercuts our position on addiction."[541] Ultimately, BAT Industries rejected the purchase of Stowic.

iv. The Wigand Deposition. A comment from public health organizations has also urged FDA to consider a 1995 deposition of Jeffrey S. Wigand, the vice president of research and development at Brown & Williamson from 1989 to 1993. According to Wigand's deposition, which was submitted to the Agency with the comment, and which has been widely publicized in the media, a number of officers of Brown & Williamson, including Thomas Sandefur, the company president and chief executive officer, made "numerous statements . . . that *we're in the nicotine delivery business.*"[542] Wigand also testified in the deposition that Sandefur "frequently" stated the opinion and belief that nicotine is "*addictive*";[543] that Brown & Williamson manipulates nicotine levels in tobacco, using various techniques including blending of tobacco leaves and adding ammonia compounds to change the pH of smoke;[544] that BATCO scientists had done studies to identify "the boundaries of nicotine pharmacology," and that BATCO showed that nicotine below "0.4 milligrams does not sustain satisfaction."[545]

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[541] McGraw M (Brown & Williamson), *Nicotine Delivery Systems* (Apr. 24, 1992), at 1-2 (emphasis added). *See* AR (Vol. 531 Ref. 124).

[542] Deposition transcript of Wigand JS (Nov. 29, 1995), at 12 (emphasis added). *See* AR (Vol. 700 Ref. 224, exhibit 2).

[543] *Id.* at 12-13.

[544] *Id.* at 27-29.

[545] *Id.* at 27, 33.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

Wigand's assertions in the deposition have been disputed by Brown & Williamson, which contends that they are untrue.[546] His statements, however, are consistent with and corroborated by the views expressed by Brown & Williamson and BAT Industries officials since the 1960's. Although the Agency finds Wigand's testimony to be additional relevant evidence of the manufacturers' intent to affect the structure and function of the body, his testimony is not essential to any of the Agency's determinations.

Cumulatively, the three decades of documents from Brown & Williamson, BATCO, and BAT Industries demonstrate that these companies have long understood that nicotine is addictive and has other significant pharmacological effects; that consumers smoke cigarettes to obtain the drug effects of nicotine; and that cigarettes are a drug delivery system, functioning as "the means of providing nicotine in a metered fashion."[547]

d. The Statements and Research of Other Cigarette Manufacturers

The administrative record establishes that the other major cigarette companies, the American Tobacco Company, the Lorillard Tobacco Company, and the Liggett Group Inc., funded research studies similar to the research conducted by Philip Morris, RJR, and Brown & Williamson, and as a result of the research have acquired a detailed knowledge of the pharmacological effects of nicotine on the brain.

For instance, American Tobacco which merged with Brown & Williamson in 1995, funded extensive research on nicotine pharmacology. From 1940 through 1970, American

[546] *See, e.g.*, Freedman AM. Cigarette defector says CEO lied to Congress about view of nicotine, *Wall Street Journal*, Jan. 26, 1996. *See* AR (Vol. 639 Ref. 2).

[547] Proceedings of BATCO Group R&D Smoking Behaviour Marketing Conference, Session I (Jul. 9-12, 1984) (slide), at BW-W2-03242. *See* AR (Vol. 24 Ref. 316).

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Tobacco funded 111 studies on the biological effects of cigarettes.[548] According to a staff report of the House Subcommittee on Health and the Environment, ninety-three of these studies (over 80%) related to the effects of nicotine on the body.[549] In one 1945 study funded by the company, entitled "The Role of Nicotine in the Cigarette Habit," smokers were given cigarettes with extremely low levels of nicotine. The study found that half of the subjects "definitely missed the nicotine."[550]

The activities of the Council for Tobacco Research (CTR), an industry trade association that conducts research on behalf of the major tobacco producers in the United States,[551] are further evidence of the extent of the industry's knowledge of the pharmacological effects of nicotine on the human brain. On behalf of the tobacco industry, CTR has funded numerous studies on the pharmacology of nicotine. The goal of these studies was to learn why nicotine makes people want to smoke:

> Most of the pharmacological studies currently being supported by The Council are concerned with the effects of nicotine and/or smoking on the central nervous system (the brain) with *the object of learning more about why people like, want or need to smoke.*[552]

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[548] Staff Report, *Evidence of Nicotine Manipulation by the American Tobacco Company*, and exhibits, prepared by the Majority Staff Subcommittee on Health and the Environment (Dec. 20, 1994), at 3. *See* AR (Vol. 292 Ref. 4064-4066).

[549] *Id.*

[550] Finnegan JK, Larson PS, Haag HB (American Tobacco Co.). The role of nicotine in the cigarette habit, in *Biologic Research on Tobacco* (American Tobacco Company: 1962), at 65-66 (originally published in *Science* 1945;102). *See* AR (Vol. 14 Ref. 178-1).

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[552] Council for Tobacco Research, *Report of the Scientific Director, 1969-1970*, at 13 (emphasis added). *See* AR (Vol. 16 Ref. 195-4).

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II.C.2.

The body of CTR research on nicotine pharmacology is extensive. For example:

- Thirty-nine CTR studies identify the sites and mechanisms of nicotine receptors in the brain;[553]

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[553] These CTR documents, along with the other CTR documents cited in this section, can be found in the administrative record, Volumes 45-64 of Docket 95N0253J:

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- Nine CTR studies show that nicotine induces both arousal and calming effects;[556]

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- Nine CTR studies use an EEG to examine the effects of nicotine on brain waves;[557]
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- Six CTR studies characterize the effect of nicotine on behavioral performance and cognitive function;[559]
- Six CTR studies research the general pharmacokinetics of nicotine; [560]

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- Five CTR studies describe the development of sophisticated techniques for determining the presence of nicotine in body fluids;[561]
- Four CTR studies evaluate plasma profiles of nicotine;[562]

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[560] Becker RF, King JE, Studies on nicotine absorption during pregnancy. II. The effects of acute heavy doses on mother and neonates, *Am J Obstet Gynecol* 1966;95(4):515-522.

Haines CF Jr, Mahajan DK, Miljkovc D, *et al.*, Radioimmunoassay of plasma nicotine in habituated and naive smokers, *Clin Pharmacol Ther* 1974;16(6):1083-1089.

Hibberd AR, Gorrod JW, Enzymology of the metabolic pathway from nicotine to cotinine, in vitro, *Eur J Drug Metab Pharmacokinet* 1983;8:151-162.

Kershbaum A, Bellet S, Cigarette, cigar, and pipe smoking. Some differences in biochemical effects, *Geriatrics* 1968;23(3):126-134.

Monji N, Castro A, Plasma nicotine pharmacokinetics in dogs after intravenous administration: determination by radioimmunoassay, *Res Commun Chem Pathol Pharmacol* 1979;23(2):267-277.

Rama Sastry BV, Chance MB, Singh G, *et al.*, Distribution and retention of nicotine and its major metabolize cotinine in the rat as a function of time, in *International Symposium on Nicotine*, eds. Clarke PBS, Quik M, Thurau K, *et al.*, 1994:125.

[561] Castro A, Monji N, Nicotine enzyme immunoassay, *Res Commun Chem Pathol Pharmacol* 1986; 51(3):393-404.

Castro A, Malkus H, Radioimmunoassays of drugs of abuse in humans: a review, *Res Commun Chem Pathol Pharmacol* 1977;16(2):291-309.

Haines CF Jr, Mahajan DK, Miljkovc D, *et al.*, Radioimmunoassay of plasma nicotine in habituated and naive smokers, *Clin Pharmacol Ther* 1974;16(6):1083-1089.

McNiven NL, Raisinghani KH, Patashnik S, *et al.*, Determination of nicotine in smokers' urine by gas chromatography, *Nature* 1965;208:788-789.

Monji N, Castro A, Plasma nicotine pharmacokinetics in dogs after intravenous administration: determination by radioimmunoassay, *Res Commun Chem Pathol Pharmacol* 1979;23(2):267-277.

[562] Castro A, Monji N, Nicotine enzyme immunoassay, *Res Commun Chem Pathol Pharmacol* 1986; 51(3):393-404.

Haines CF Jr, Mahajan DK, Miljkovc D, *et al.*, Radioimmunoassay of plasma nicotine in habituated and naive smokers, *Clin Pharmacol Ther* 1974;16(6):1083-1089.

Monji N, Castro A, Plasma nicotine pharmacokinetics in dogs after intravenous administration: determination by radioimmunoassay, *Res Commun Chem Pathol Pharmacol* 1979;23(2):267-277.

Rama Sastry BV, Chance MB, Singh G, *et al.*, Distribution and retention of nicotine and its major metabolize cotinine in the rat as a function of time, in *International Symposium on Nicotine*, eds. Clarke PBS, Quik M, Thurau K, *et al.*, 1994:125.

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- Four CTR studies research the factors affecting the onset and duration of nicotine's effects on the body;[563]
- Three CTR studies investigate the metabolic fate of nicotine;[564]
- Two CTR studies specifically investigate the enzymatic systems involved in nicotine metabolism;[565]
- Two CTR studies show that smokers metabolize nicotine faster than nonsmokers;[566]
- Two CTR studies examine the factors affecting the absorption of nicotine into the bloodstream;[567]

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[563] Domino EF, Electroencephalographic and behavioral arousal effects of small doses of nicotine: A neuropsychopharmacological study. The effects of nicotine and smoking on the central nervous system, *Ann N Y Acad Sci* 1967;142:216-244.

Hoff EC, Hockman CH, Neurophysiological aspects of the action of nicotine. The effects of nicotine and smoking on the central nervous system, *Ann N Y Acad Sci* 1967;142:121-125.

Lapin EP, Maker HS, Sershen H, *et al.*, Dopamine-like action of nicotine: lack of tolerance and reverse tolerance, *Brain Res* 1987;407(2):351-363.

Stitzer M, Morrison J, Domino EF, Effects of nicotine on fixed-interval behavior and their modification by cholinergic antagonists, *J Pharmacol Exp Ther* 1970;171(2):166-177.

[564] Abood LG, Grassi S, Junig J, *et al.*, Specific binding and metabolism of (-)- and (+)-[3H] nicotine in isolated rat hepatocytes and hepatocyte membranes, *Arch Int Pharmacodyn Ther* 1985;273(1):62-73.

Hibberd AR, Gorrod JW, Nicotine delta 1 '(5)' iminium ion: a reactive intermediate in nicotine metabolism, *Adv Exp Med Biol* 1981;1121-1131.

Vincek WC, Martin BR, Aceto MD, *et al.*, Synthesis of 4,4-diritio-(+)-nicotine: comparative binding and distribution studies with natural enantiomer, *J Pharm Sci* 1981;70(11):1292-1293.

[565] Hibberd AR, Gorrod JW, Enzymology of the metabolic pathway from nicotine to cotinine, in vitro, *Eur J Drug Metab Pharmacokinet* 1983;8:151-162.

Wilson KL Jr, Chang, RS, Bowman ER, *et al.*, Nicotine-like actions of cis-metanicotine and trans-metanicotine, *J Pharmacol Exp Ther* 1976;196(3):685-696.

[566] Hatchell PC, Collins AC, The influence of genotype and sex on behavioral sensitivity to nicotine in mice, *Psychopharmacology (Berl)* 1980;71(1):45-49.

Jusko WJ, Role of tobacco smoking in pharmacokinetics, *J Pharmacokinet Biopharm* 1978;6(1):7-39.

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- Two CTR studies examine the distribution of nicotine to the brain;[568]
- Two CTR studies research the relationship of nicotine's physiological effects on the body to nicotine blood levels;[569] and
- One CTR study shows that there may be gender differences in the metabolism of nicotine.[570]

The results of the CTR-funded research show that nicotine has significant pharmacological effects on the body. In fact, numerous CTR studies demonstrate that nicotine produces pharmacological effects similar to those of other addictive substances. For example:

- Thirteen CTR studies demonstrate that nicotine, like other addictive drugs, acts on dopaminergic receptors in the brain to release dopamine, a chemical in the brain's reward system that reinforces the intake of certain substances;[571]

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[567] Haines CF Jr, Mahajan DK, Miljkove D, *et al.*, Radioimmunoassay of plasma nicotine in habituated and naive smokers, *Clin Pharmacol Ther* 1974;16(6):1083-1089.

Kershbaum A, Bellet S, Cigarette, cigar, and pipe smoking. Some differences in biochemical effects, *Geriatrics* 1968;23(3):126-134.

[568] Hatchell PC, Collins AC, The influence of genotype and sex on behavioral sensitivity to nicotine in mice, *Psychopharmacology (Berl)* 1980;71(1):45-49.

Vincek WC, Martin BR, Aceto MD, *et al.*, Synthesis of 4,4-dinitio-(+)-nicotine: comparative binding and distribution studies with natural enantiomer, *J Pharm Sci* 1981;70(11):1292-1293.

[569] Hatchell PC, Collins AC, The influence of genotype and sex on behavioral sensitivity to nicotine in mice, *Psychopharmacology (Berl)* 1980;71(1):45-49.

Westfall TC, Anderson GP, Influence of nicotine on catecholamine metabolism in the rat, *Arch Int Pharmacodyn Ther* 1967;169(2):421-428.

[570] Jusko WJ, Role of tobacco smoking in pharmacokinetics, *J Pharmacokinet Biopharm* 1978;6(1):7-39.

[571] Abood LG, Lu X, Banerjee S, Receptor binding characteristics of a 3H-labeled azetidine analogue of nicotine, *Biochem Pharmacol* 1987;36(14):2337-2341.

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- Twelve CTR studies demonstrate that tolerance to nicotine occurs;[572]

Andersson K, Fuxe K, Eneroth P, *et al.*, Mecamylamine induced blockade of nicotine induced inhibition of gonadotrophin and TSH secretion and of nicotine induced increases of catecholamine turnover in the rat hypothalamus. *Acta Physiol Scand Suppl* 1980;479:27-29.

Andersson K, Fuxe K, Eneroth P, *et al.*, Effects of acute intermittent exposure to cigarette smoke on catecholamine levels and turnover in various types of hypothalamic DA and NA nerve terminal systems as well as on the secretion of adenohypophyseal hormones and corticosterone. *Acta Physiol Scand* 1985;124(2):277-285.

Andersson K, Fuxe K, Eneroth P, *et al.*, Involvement of cholinergic nicotine-like receptors as modulators of amine turnover in various types of hypothalamic dopamine and noradrenaline nerve terminal systems and of prolactin, LH, FSH and TSH secretion in the castrated male rat. *Acta Physiol Scand* 1982;116(1):41-50.

Andersson K, Fuxe K, Eneroth P, *et al.*, Interactions of nicotine and pentobarbitone in the regulation of telencephalic and hypothalamic catecholamine levels and turnover and of adenohypophyseal hormone secretion in the normal male rat. *Naunyn Schmiedabergs Arch Pharmacol* 1982;321(4):287-292.

Andersson K, Fuxe K, Eneroth P, *et al.*, Effects of acute central and peripheral administration of nicotine on hypothalamic catecholamine nerve terminal systems and on the secretion of adenohypophyseal hormones in the male rat. *Med Biol* 1982;60(2):98-111.

Erwin VG, Cornell K, Towell JF, Nicotine alters catecholamines and electrocortical activity in perfused mouse brain. *Pharmacol Biochem Behav* 1986;24(1):99-105.

Fuxe K, Andersson K, Harfstrand A, *et al.*, Increases in dopamine utilization in certain limbic dopamine terminal populations after a short period of intermittent exposure of male rats to cigarette smoke. *J Neural Transm* 1986;67(1-2):15-29.

Grenhoff J, Svensson TH, Selective stimulation of limbic dopamine activity by nicotine. *Acta Physiol Scand* 1988;133(4):595-596.

Harsing LG, Sershen H, Vizi SE, *et al.*, N-type calcium channels are involved in the dopamine releasing effect of nicotine. *Neurochem Res* 1992;17(7):729-734.

Lapin EP, Maker HS, Sershen H, *et al.*, Action of nicotine on accumbens dopamine and attenuation with repeated administration. *Eur J Pharmacol* 1989;160(1):53-59.

Lapin EP, Maker HS, Sershen H, *et al.*, Dopamine-like action of nicotine: lack of tolerance and reverse tolerance. *Brain Res* 1987;407(2):351-363.

Westfall TC, Effect of nicotine and other drugs on the release of 3H-norepinephrine and 3H-dopamine from rat brain slices, *Neuropharmacology* 1974;13(8):693-700.

[573] Abood LG, Lowy K, Booth H, Acute and chronic effects of nicotine in rats and evidence for a non-cholinergic site of action. *NIDA Res Monogr* 1979:136-149.

Abood LG, Grassi S, Costanzo M, *et al.*, Behavioral and biochemical studies in rats after chronic exposure to nicotine. *NIDA Res Monogr* 1984;54:348-355.

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II.C.2.

- Three CTR studies research the neurochemical mechanisms of nicotine withdrawal;[573]

Andersson K, Fuxe K, Eneroth P, *et al.*, Effects of withdrawal from chronic exposure to cigarette smoke on hypothalamic and preoptic catecholamine, nerve terminal systems . and on the secretion of pituitary hormones in the male, *Naunyn Schmiedebergs Arch Pharmacol* 1989;339(4):387-396.

Cronan T, Conrad J, Bryson R, Effects of chronically administered nicotine and saline on motor activity in rats, *Pharmacol Biochem Behav* 1985;22(5):897-899.

Domino EF, Lutz MP, Tolerance to the effects of daily nicotine on rat bar pressing behavior for water reinforcement, *Pharmacol Biochem Behav* 1973; 1(4):445-448.

Fuxe K, Andersson K, Eneroth P, *et al.*, Effects of Nicotine and exposure to cigarette smoke on discrete dopamine and noradrenaline nerve terminal systems of the telencephalon and diencephalon of the rat: Relationship to reward mechanisms and neuroendocrine functions and distribution of nicotinic binding sites in brain, in *Tobacco Smoking and Nicotine: A Neurobiological Approach*, eds. Martin WR, Van Loo GR, Iwamoto ET, *et al.*, 1987:225-262.

Lapin EP, Maker HS, Sershen H, *et al.*, Dopamine-like action of nicotine: lack of tolerance and reverse tolerance, *Brain Res* 1987;407(2):351-363.

Nelsen JM, Goldstein L, Improvement of performance on an attention task with chronic nicotine treatment in rats, *Psychopharmacologia* 1972;26(4):347-360.

Rosecrans JA, Noncholinergic mechanisms involved in the behavioral and stimulus effects of nicotine, and relationships to the process of nicotine dependence, in *Tobacco Smoking and Nicotine: A Neurobiological Approach*, eds. Martin WR, Van Loo GR, Iwamoto ET, *et al.*, 1987:125-139.

Stitzer M, Morrison J, Domino EF, Effects of nicotine on fixed-interval behavior and their modification by cholinergic antagonists, *J Pharmacol Exp Ther* 1970;171(2):166-177.

Wenzel DG, Azmeh N, Clark II, Studies on the acute and chronic depressor actions of nicotine in the rat, *Arch int Pharmacodyn Ther* 1971;193(1):23-36.

Westfall TC, Brase DA, Studies on the mechanism of tolerance to nicotine-induced elevations of urinary catecholamines, *Biochem Pharmacol* 1971;20(7):1627-1635.

[573] Andersson K, Effects of withdrawal from chronic exposure to cigarette smoke on hypothalamic and preoptic catecholamine nerve terminal systems and the secretion of pituitary hormones in the male, *Naunyn Schmiedebergs Arch Pharmacol* 1989;339(4):387-396.

Fuxe K, Effects of Nicotine and exposure to cigarette smoke on discrete dopamine and noradrenaline nerve terminal systems of the telencephalon and diencephalon of the rat: relationship to reward mechanisms and neuroendocrine functions and distribution of nicotinic binding sites in brain, in *Tobacco Smoking and Nicotine: A Neurobiological Approach*, eds. Martin WR, Van Loo GR, Iwamoto ET, *et al.*, 1987:225-262.

Rosecrans JA, Noncholinergic mechanisms involved in the behavioral and stimulus effects of nicotine, and relationships to the process of nicotine dependence, in *Tobacco Smoking and Nicotine: A Neurobiological Approach*, eds. Martin WR, Van Loo GR, Iwamoto ET, *et al.*, 1987:125-139.

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- Two CTR studies investigate the effects of nicotine withdrawal on performance;[574]
- Two CTR studies show that nicotine is psychoactive and produces clearly discriminable stimulus effects;[575] and
- Two CTR studies show that nicotine can enhance the rewarding effects of electrical brain stimulation.[576]

Indeed, seven CTR studies state expressly that nicotine is an addictive or dependence-producing drug.[577] For instance, one CTR-funded study stated that "*smoking*

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[574] Heimstra NW, Fallesen JJ, Kinsley SA, *et al.*, The effects of deprivation of cigarette smoking on psychomotor performance, *Ergonomics* 1980;23(11):1047-1055.

Heimstra NW, Bancroft NR, DeKock AR, Effects of smoking upon sustained performance in a simulated driving task, in the effects of nicotine and smoking on the central nervous system, *Ann NY Acad Sci* 1967;142:295-307.

[575] Chance WT, Kallman MD, Rosecrans JA, *et al.*, A comparison of nicotine and structurally related compounds as discriminative stimuli, *Br J Pharmacol* 1978;63(4):609-616.

Rosecrans JA, Nicotine as a discriminative stimulus: a neurobehavioral approach to studying central cholinergic mechanisms, *J Subst Abuse* 1989;1(3):287-300.

[576] Olds ME, Domino EF, Comparison of muscarinic and nicotinic cholinergic agonists on self-stimulation behavior, *J Pharmacol Exp Ther* 1969;166(2):189-204.

Pradhan SN, Bowling C, Effects of nicotine on self-stimulation in rats, *J Pharmacol Exp Ther* 1971;176(1):229-243.

Deneau GA, Inoki R, Nicotine self-administration in monkeys, in The effects of nicotine and smoking on the central nervous system, *Ann N Y Acad Sci* 1967;142:277-279.

Other research jointly funded by the tobacco industry examines nicotine's ability to serve as a positive reinforcer in self-administration studies involving monkeys. *See* 60 FR 41642.

[577] Bouse R Gamery AJ, Glynn RJ, Age and addiction to smoking, *Addict Behav* 1980;5(4):341-351.

Martin WR, Van Loo GR, Iwamoto ET, *et al.*, *Tobacco Smoking and Nicotine: A Neurobiological Approach* (New York: Plenum Press, 1987).

Rosecrans JA, Noncholinergic mechanisms involved in the behavioral and stimulus effects of nicotine, and relationships to the process of nicotine dependence, in *Tobacco Smoking and Nicotine: A Neurobiological Approach*, eds. Martin WR, Van Loo GR, Iwamoto ET, *et al.*, 1987:125-139.

Rosecrans JA, Nicotine as a discriminative stimulus: a neurobehavioral approach to studying central cholinergic mechanisms, *J Subst Abuse* 1989;1(3):287-300.

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is a form of dependence no less binding than that of other addictive drugs."[578] Similarly, another CTR-funded study observed that "*compelling evidence now exists that regular smoking is a form of drug addiction to nicotine.*"[579]

The Agency received no comments disputing FDA's characterization in the Jurisdictional Analysis of any of these CTR-funded studies. Thus, these uncontested studies demonstrate that the entire cigarette industry had detailed knowledge of the pharmacological effects of nicotine on the brain, including knowledge of research funded by the industry that found nicotine to be an addictive drug.

Collectively, these CTR studies and the studies conducted by individual cigarette manufacturers show that the cigarette manufacturers have acted like traditional pharmaceutical companies. Before marketing a prescription drug, a pharmaceutical company studies the pharmacokinetics of the drug (how it is absorbed into the body, metabolized, and excreted), the pharmacodynamics of the drug (what specific effects the drug has on the body's chemistry and metabolism as it makes its way through the body), and the clinical effects of the drug (whether the drug is effective in producing the desired

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Svensson TH, Grenhoff J, Engberg G. Effect of nicotine on dynamic function of brain catecholamine neurons, in *The Biology of Nicotine Dependence*, eds. Bock G, Marsh J, *CIBA Foundation Symposium* 1990;152:169-180.

Tung CS, Ugedo L, Grenhoff J, *et al.*, Peripheral induction burst firing in locus coeruleus neurons by nicotine mediated via excitatory amino acids, *Synapse* 1989;4(4):313-318.

Williams JS, Crumpacker DW, Krier MJ, Stability of a factor-analytic description of smoking behavior, *Drug Alcohol Depend* 1980;5(6):467-478.

[578] Boase R Gamery AJ, Glynn RJ, Age and addiction to smoking, *Addict Behav* 1980;5(4):341-351 (emphasis added).

[579] Svensson TH, Grenhoff J, Engberg G, Effect of nicotine on dynamic function of brain catecholamine neurons, in The *Biology of Nicotine Dependence*, eds. Bock G, Marsh J, *CIBA Foundation Symposium* 1990;152:169-180 (emphasis added).

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therapeutic or physiological effects). The cigarette manufacturers have conducted or funded the same studies for nicotine. As a result, the cigarette manufacturers' understanding of the pharmacological effects and uses of nicotine are closely analogous to—if not more extensive and sophisticated than—the understanding any pharmaceutical company has of traditional drug products.

e. Three Decades of Statements and Research by Cigarette Manufacturers Are Sufficient to Establish Intent

As discussed in section II.C.1., above, the statements and research of a manufacturer are relevant evidence of the uses of a product that are "intended" by the manufacturer. This evidence shows that when the manufacturers offer cigarettes for sale, they "have in mind" that their products will be purchased for specific pharmacological uses by consumers. Hence, the evidence is sufficient to establish that the effects of cigarettes on the structure and function of the body are "intended" by the manufacturers.

The cigarette manufacturers assert, however, that the statements and research relied upon by the Agency are not reliable evidence of the cigarette manufacturers' intent in this case. Among other things, they argue that the three decades of tobacco company statements and research on the addictive and other pharmacological effects of nicotine contained in the administrative record are irrelevant to the intended use of cigarettes and smokeless tobacco because the statements were made and the research was conducted over a period of many years and are not contemporaneous with the sale of currently marketed products.[580]

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[580] Other arguments of the manufacturers concerning the evidence that may be used to establish intended use are addressed in section II.E., below.

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FDA disagrees. The extensiveness of the statements and research of the cigarette manufacturers in the administrative record, most of which have only recently become available, reflects a remarkably consistent pattern of the industry's views, repeated frequently over time. These documents and statements establish the knowledge and belief of tobacco company officials that cigarettes have, and are predominantly used by consumers for, pharmacological effects. The fact that these statements span three decades simply demonstrates that the companies' knowledge and beliefs about the pharmacological effects and uses of cigarettes are both long-standing and consistent. As described in section II.A.5., above, commercial cigarettes marketed today contain a level of nicotine that is sufficient to produce addiction and other pharmacological effects. Thus, statements made 30 years ago about the pharmacological effects of nicotine in cigarettes are equally relevant to the cigarettes being marketed today. Moreover, as discussed above, many of the statements and research relied upon by FDA are of recent origin.

Tobacco industry comments also argue that statements of individuals employed, or formerly employed, by the manufacturers are not relevant to establishing the intent of any manufacturer because they are not formal statements of company policy. According to one manufacturer's comments, the only statements that are evidence of the manufacturer's "institutional intent" are those that have been adopted by the manufacturer "after whatever formalities required by the decision-making procedures of the institution have been followed."[581]

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[581] R.J. Reynolds Tobacco Co., Comment (Jan. 2, 1996), at 24. *See* AR (Vol. 519 Ref. 103).

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FDA disagrees that the statements of tobacco industry employees are not evidence of the intended use of the product. FDA is relying on the statements as evidence that the tobacco companies know that nicotine in tobacco has pharmacological effects and that consumers use tobacco to obtain those effects. Many of the statements come from executives at the companies. As one court observed, in a case relied upon by a tobacco company comment:

> When a major company executive speaks, "everybody listens" in the corporate hierarchy, and when an executive's comments prove to be disadvantageous to a company's subsequent litigation posture, it cannot compartmentalize this executive as if he had nothing more to do with company policy than the janitor or watchman.

Ezold v. Wolf, 983 F.2d 509, 546 (3d Cir. 1992) (internal citation omitted).

Moreover, many of the statements relied upon by FDA come from individuals whose function within the company was to research and understand the motives for smoking and who regularly communicated those views to company management. A corporation ordinarily relies on its research department to answer scientific questions, such as the pharmacologic effects of its product on users and the purposes for which consumers use the product. The statements quoted by FDA show a highly consistent pattern of views within and among the research departments of the cigarette companies, demonstrating that the statements are not the idiosyncratic opinions of a few individuals within one company, but widely shared views.

Indeed, the record shows that the cigarette manufacturers did in fact rely upon and regularly consult with their research scientists. In the case of Philip Morris, for instance, the CEO of Philip Morris, the president of Philip Morris USA, and vice presidents and directors from functions such as marketing met on a monthly basis with senior officials and

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scientists from the company's research and development department to discuss Philip Morris' basic and applied research and other topics.[582] These regular meetings, the occurrence of which Philip Morris does not dispute, show that the knowledge and views of the Philip Morris scientists were regularly sought by and communicated to the officers at the head of the company.

For these reasons, the statements and research of the cigarette manufacturers are sufficient evidence to establish that the manufacturers intend to affect the structure and function of the body. As FDA's regulations recognize, "objective intent" can be established by evidence that "a manufacturer knows, or has knowledge of, facts that would give him notice," that a product will be used for pharmacological purposes. 21 CFR 201.128, 801.4.[583]

3. The Cigarette Manufacturers Have Conducted Extensive Product Research and Development To Optimize the Delivery of Nicotine

The tobacco industry documents in the administrative record show not only that the cigarette manufacturers "have in mind" that cigarettes will be used for specific pharmacological purposes, but also that they have "designed" cigarettes to ensure that smokers receive a pharmacologically active dose of nicotine. The evidence in the record contains two categories of evidence of the manufacturers' design: (1) the evidence of the

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[582] Declaration of Uydess IL (Feb. 29, 1996), at 22-23. *See* AR (Vol. 638 Ref. 1).

[583] The Freedom of Information Act (FOIA) and Title VII cases cited by the comments do not purport to set forth a standard for assessing objective intent under public health statutes like the Federal Food, Drug, and Cosmetic Act, and the two statutes serve different purposes than the Act. They are, therefore, not controlling here. The FDA regulation cited by the comments is similarly inapplicable to the question of what evidence is relevant to establishing intended use. FDA is not contending that the statements of a single tobacco company employee can bind the company in such a way that the totality of the remaining evidence of intent can be overridden. Here, however, there is a consistent pattern of internal statements that, taken as a whole, are highly relevant to intent.

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manufacturers' extensive product research and development to identify the doses of nicotine needed to produce pharmacological effects and to optimize the delivery of nicotine to smokers, which is discussed below; and (2) the evidence of the manufacturers' control and manipulation of nicotine in marketed cigarettes, which is discussed in section II.C.4., below.

The product research and development efforts described in the administrative record indicate that for three decades the cigarette manufacturers have strived to develop ways to maintain pharmacologically active doses of nicotine despite consumer demands for "healthier," lower-yield products. A primary focus of the cigarette manufacturers' efforts has been to deliver sufficient nicotine to provide the desired pharmacological effects of nicotine while at the same responding to consumer health concerns by reducing tar deliveries. Industry documents disclose research to determine the dose of nicotine that must be delivered to ensure "pharmacological satisfaction,"[584] as well as estimates by company scientists of the range of acceptable nicotine doses to produce pharmacological effects. These documents show that the manufacturers are aware that consumers will not accept cigarettes that do not deliver a pharmacologically active dose of nicotine.

The manufacturers' product research and development efforts have involved a wide variety of approaches to ensure delivery of an adequate dose of nicotine, including changes in tobacco blends; chemical manipulation to liberate "free" nicotine; filter and ventilation designs that selectively remove more tar than nicotine; the development of high-technology nicotine delivery devices that provide smokers nicotine but virtually no

[584] BATCO Group R&D Research Programme. 1984: Proposed revisions for 1985-87. Research Conference. Southampton, England (Sep. 1984), at 2. *See* AR (Vol. 26 Ref. 369-1).

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tar; genetic engineering of tobacco plants to enhance nicotine content; the search for nicotine "analogues" that retain nicotine's reinforcing abilities; and research into compounds that act synergistically to strengthen nicotine's pharmacological effects. As discussed in section II.C.4., below, many (but not all) of these methods are used in cigarettes currently marketed to the public.[585]

a. Philip Morris' Product Research and Development Efforts

Evidence on the research and development efforts of Philip Morris demonstrates that the company believes that cigarettes must deliver sufficient nicotine to produce pharmacological effects in smokers and that the company conducted extensive research to optimize nicotine delivery from its cigarettes.

In a 1972 document, Philip Morris senior scientist William Dunn discussed the basis for the company's concerns about lowering nicotine levels below a certain minimum. Dunn related consumers' lack of interest in cigarettes providing less than 1 mg of nicotine to the fact that 1 mg of nicotine "readily" produces the desired "physiological response":

> Despite many low nicotine brand entries into the marketplace, none of them have captured a substantial segment of the market. In fact, critics of the industry would do well to reflect upon the indifference of the consumer to the industry's efforts to sell low-delivery brands. 94% of the cigarettes sold in the U.S. deliver more than 1 mg of nicotine. 98.5% deliver more than 0.9 mg.[586] *The physiological response to nicotine can readily be elicited by cigarettes delivering in the range of 1 mg of nicotine.*[587]

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[585] The evidence discussed in section II.C.3. is also relevant to, and provides further support for, the Agency's finding that the cigarette manufacturers "have in mind" that their products will be used for pharmacological purposes.

[586] Dunn WL., *Motives and Incentives in Cigarette Smoking* (1972) (summary of CTR-sponsored conference in St. Martin), at 4. *See* AR (Vol. 12 Ref. 133).

[587] *Id.* (emphasis added).

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A 1978 Philip Morris document shows a similar focus on identifying the minimum amount of nicotine necessary to produce pharmacological effects, referred to as the threshold level of nicotine in the body that satisfies consumers' "nicotine need."[588] The document discussed plans to study cigarettes in which the tar level was kept constant, but the nicotine level was varied. The purpose of the study was to determine how smokers react to levels of nicotine so close to the minimum that "the total nicotine in the [smoker's] system remains at or near the nicotine need threshold."[589]

This focus on producing cigarettes that provide pharmacologically active doses of nicotine is a prominent feature of Philip Morris' development of low-tar cigarettes. William Farone, the former director of applied research at Philip Morris, described the goals of Philip Morris' product research and development efforts in a statement submitted to the Agency. According to Farone, "*a key objective of the cigarette industry over the last 20-30 years*" was decreasing tar while maintaining the delivery of nicotine, and that tobacco company researchers therefore considered it a "top priority" to "[m]inimiz[e] the exposure to the potential negative health effects of the undesirable chemical components in tar *while maintaining an acceptable and pharmacologically active nicotine level.*"[590] This involved extensive product research and development. Farone stated:

> Extensive, in some instances ground breaking, research by the tobacco industry was necessary to construct a cigarette that ensured an adequate delivery of nicotine as the cigarette market evolved from the traditional full flavored, unfiltered product of the

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[588] Dunn WL, *Plans and Objectives–1979* (Dec. 6, 1978), in 141 Cong. Rec. H7670 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[589] *Id.*

[590] Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 4 (emphasis added). *See* AR (Vol. 638 Ref. 2).

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> 1950's to the filtered, low tar cigarette demanded by many smokers for the last 30-40 years. *The objective of industry scientists and product developers, simply stated, was to provide the consumer with the same pharmacological satisfaction derived from nicotine* in the natural blends and flavor of the full strength cigarettes of the 1950's as the marketplace shifted to the naturally less flavorful and satisfying low tar and nicotine cigarette demanded by the more health conscious consumer.[591]

The declaration of Ian Uydess, an associate senior scientist at Philip Morris from 1977 to 1989, confirms the company's extensive interest in nicotine delivery. According to Uydess, "*Philip Morris wanted to know everything there was to know about nicotine.*"[592] Sophisticated equipment, such as liquid and gas chromatographs, mass spectrometers, infra-red spectrometers, and nuclear magnetic resonance instruments, was acquired by Philip Morris to research questions such as:

> (1) How nicotine levels varied in the tobacco plant with regard to cultivar, stalk position, seasonal variations and 'ripeness,' (2) What happened to nicotine after 'curing' and during processing, (3) What chemical 'forms' was it in, and (4) How much of it wound up in the smoke when burned under different conditions (such as . . . in the presence . . . of varying amounts of other tobacco constituents, etc.).[593]

The evidence in the administrative record shows that to achieve the goal of maintaining an acceptable and pharmacologically active nicotine level, Philip Morris developed ways to manipulate the ratio of nicotine to tar delivered by the cigarette. This

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[591] *Id.* at 7 (emphasis added). These statements and those by another former Philip Morris employee discussed below corroborate the other evidence before the Agency indicating that the tobacco industry conducted extensive research on nicotine levels.

[592] Declaration of Uydess II. (Feb. 29, 1996), at 14 (emphasis added). *See* AR (Vol. 638 Ref. 1).

[593] *Id.* at 14.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

research was conducted in the 1970's and had as its goal "to determine what combinations of tar and nicotine make for optimal acceptability in a low delivery cigarette."[594]

The nicotine/tar ratio in cigarettes compares the amount of nicotine delivered by a cigarette with the amount of tar delivered by the cigarette. In public statements, officials of the tobacco industry have maintained that, as tar levels have been reduced through techniques such as filtration and ventilation, nicotine levels have been automatically reduced by a corresponding amount. For instance, one industry executive testified before Congress in 1994, "[w]e do not set levels of nicotine for particular brands of cigarettes. Nicotine follows the tar levels. . . . The correlation . . . is essentially perfect correlation between tar and nicotine and shows that there is no manipulation of nicotine."[595] Thus, according to the cigarette manufacturers, a proportional reduction of tar and nicotine demonstrates that the industry has not manipulated nicotine deliveries.

The goal of Philip Morris' research, however, was to determine whether cigarette acceptability could be improved by changing this "essentially perfect correlation" between tar and nicotine, i.e., by allowing tar to fall but maintaining a *disproportionately* high level

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[594] Dunn WL, *et al.* (Philip Morris Inc.), *Plans for 1972* (Sep. 8, 1971), in 141 Cong. Rec. H8128 (daily ed. Aug. 1, 1995). *See* AR (Vol. 711 Ref. 6).

There is evidence that Philip Morris' product research and development on maintaining adequate nicotine deliveries may have begun before the 1970's. A comment submitted to the Agency the handwritten notes of a Philip Morris research executive, Ronald A. Tamol. According to 1965 note from Tamol, an objective of his research at that time was to "*determine minimum nicotine. . . to keep normal smoker 'hooked.'*" Tamol RA (Philip Morris), Handwritten Notes (Feb. 1, 1965) (emphasis added). *See* AR (Vol. 700 Ref. 593). The Agency is not relying on these notes, however, because it has not independently authenticated the notes.

[595] *Regulation of Tobacco Products (Part 1): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 143, 378 (Mar. 25, 1994) (statement of Alexander Spears). *See* AR (Vol. 707 Ref. 1).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

of nicotine. To this end, Philip Morris researchers in 1970 began to alter cigarette designs to study:

> *the effect of systematic variation of the nicotine/tar ratios upon smoking rate and acceptability measures.* Using the Marlboro as a base cigarette, *we will reduce the tar delivery incrementally by filtration and increase the nicotine delivery incrementally by adding a nicotine salt.* All cigarettes will be smoked for several days by each of a panel of 150 selected volunteers.[596]

The search for the optimal nicotine/tar ratio was a significant research priority at Philip Morris. In 1973, a 5-year research and development plan stated: "This program comprises a number of studies expected to provide insight leading to new cigaret designs. These include *studies of optimum nicotine/tar ratios, [and] nicotine/menthol relationships.*"[597]

That same year, the director of research at Philip Morris, Thomas Osdene, distributed a five-year plan stating that "R&D management will concentrate a large part of the resources at its disposal" on two "major long-range" programs, one of which was directed at achieving:

> *a dramatic reduction in cigaret tar level while maintaining the subjective responses equal to our present major brands . . . . The task requires . . . discovering which constituents contribute positively to the smoker's response . . . and . . . developing means of increasing the relative concentration of desirable constituents.*[598]

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[596] Eichorn PA, Dunn WL (Philip Morris Inc.), *Quarterly Report of Projects 1600 and 2302* (Dec. 31, 1970), in 141 Cong. Rec. H8127-8128 (daily ed. Aug. 1, 1995) (emphasis added). *See* AR (Vol. 711 Ref. 6).

[597] Philip Morris USA, *Research and Development Five Year Plan, 1974-1978* (May 1973), in 141 Cong. Rec. H8130-8131 (daily ed. Aug. 1, 1995) (emphasis added). *See* AR (Vol. 711 Ref. 6).

[598] Osdene TS (Philip Morris Inc.), *Five-Year Plan* (Oct. 29, 1973) attaching Dunn WL, Lowitz DA, Will F, *R&D Strategy Outline*, in 141 Cong. Rec. H8131-8132 (daily ed. Aug. 1, 1995) (emphasis added). *See* AR (Vol. 711 Ref. 6).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

According to the Philip Morris researchers, the natural nicotine/tar ratio in tobacco is about 0.07.[599] By 1974, the researchers found that by boosting this natural ratio to about 0.12 (i.e., by raising the level of nicotine in relation to the level of tar) they could make a low-delivery cigarette that was "comparable to the Marlboro in terms of both subjective acceptability and strength."[600] A follow-up study in 1975 also found "evidence that *the optimum nicotine to tar (N/T) ratio for a [low-delivery] tar cigarette is somewhat higher than that occurring in smoke from the natural state of tobacco.*"[601] Thus, Philip Morris' research showed that for low-tar cigarettes, it was "optimal" to supply a higher proportion of nicotine than would occur naturally. The distribution lists accompanying both the 1974 study and the 1975 follow-up show these studies were distributed to senior officials at Philip Morris, including Helmut Wakcham, the vice president for research and development.

As Philip Morris enhanced its ability to reduce tar levels, it continued to research the optimum nicotine levels to accompany these ever-lower tar levels. It also conducted research on nicotine deliveries in its competitors' low-tar brands. The Philip Morris researchers concluded that the nicotine-to-tar ratios in their competitors' products "go up as tar goes down."[602] They further stated that "the mechanics of cigarette engineering

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[599] Dunn WL, Johnston M, Ryan F, *et al.* (Philip Morris Inc.), *Plans for 1972* (Sep. 8, 1971), in 141 Cong. Rec. H8128 (daily ed. Aug. 1, 1995). *See* AR (Vol. 711 Ref. 6).

[600] Philip Morris Research Center, *Behavioral Research Annual Report (Part II)*, distributed by Osdene TS (Nov. 1, 1974), in 141 Cong. Rec. H7659 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[601] Jones B, Houck W, Martin P (Philip Morris Inc.), *Low Delivery Cigarettes and Increased Nicotine/Tar Ratios: A Replication* (Oct. 1975), in 141 Cong. Rec. H8132 (daily ed. Aug. 1, 1995) (emphasis added). *See* AR (Vol. 711 Ref. 6).

[602] Dunn WL (Philip Morris Inc.), *Plans and Objectives–1979* (Dec. 6, 1978), in 141 Cong. Rec. H7670 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

and the deliberate decisions of our competitors are such as to suggest that *high nicotine/tar ratios* be used at ultra low tar levels."[403]

This extensive research on deliberately altering nicotine/tar ratios shows that Philip Morris did not, in fact, want to allow nicotine to "follow the tar level" but instead wanted to supply an optimum nicotine level that required independent manipulation of the nicotine delivery of cigarettes. In addition to the research on optimal nicotine/tar ratios, Philip Morris scientists have conducted other product development research relating to the delivery of nicotine. In the 1980's, Philip Morris conducted extensive research to find "nicotine analogues" that could replace nicotine in cigarettes. As described in section II.C.2.a.ii., above, this research was designed to find analogues that would specifically retain nicotine's pharmacological effects on the brain, revealing both Philip Morris' recognition of the pharmacological effects of nicotine and its intent to maintain these pharmacological effects even if compelled to cease the use of nicotine.

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Philip Morris also conducted research to determine whether a second component of tobacco smoke, acetaldehyde, acted synergistically with nicotine to produce reinforcing effects on the brain. The culmination of this research was Philip Morris' attempt to establish the "maximally reinforcing" ratio of acetaldehyde to nicotine in cigarette smoke. This research demonstrates again Philip Morris' objective of identifying pharmacologically active doses of nicotine and of enhancing those effects where possible. A 1982 Philip Morris report on research plans and objectives stated:

> Since both acetaldehyde and nicotine are reinforcing agents and each are contained in smoke *it becomes important to determine ratio[s] of acetaldehyde to nicotine which produce maximal*

[403] *Id.* at H7670 (emphasis added).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

reinforcing effects . . . . This will allow us to determine the optimum ratio of acetaldehyde to nicotine that maintains the most behavior.[604]

Philip Morris' patents further reflect and corroborate its interest in developing methods of enhancing nicotine deliveries. For example, among other patents related to nicotine, Philip Morris holds patents to permit the "release in controlled amounts and when desired of nicotine"[605] and for "releasing nicotine into tobacco smoke."[606] The purpose of the patented method is to "*[m]aintain[] the nicotine content at a sufficiently high level to provide the desired physiological activity*, taste and odor which this material imparts."[607]

Collectively, the documents in the administrative record show that ensuring an adequate delivery of nicotine has been a dominant consideration in Philip Morris product research and development for nearly 30 years. As Project Table indicates, Philip Morris' research on the optimum way to deliver nicotine to smokers continues to this day. *See* section II.C.2.a.iii., above.

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[604] DeNoble VJ (Philip Morris Inc.), *Project Number 1610 (Behavioral Pharmacology) Objectives and Plans–1982-1983* (Jul. 20, 1982), at 2 (emphasis added). *See* AR (Vol. 54 Ref. 1921).

[605] U.S. Patent No. 3,280,823, Bayley A, Air B, Robb II EW, assigned to Philip Morris Inc., *Additive-Releasing Filter for Releasing Additives into Tobacco Smoke* (Oct. 25, 1966), at C2:39-40. *See* AR (Vol. 26 Ref. 352).

[606] U.S. Patent No. 3,584,630, Inskeep GE, assigned to Philip Morris Inc., *Tobacco Product Having Low Nicotine Content Associated with a Release Agent Having Nicotine Weakly Absorbed Thereon* (Jun. 15, 1971), at C2:5-15. *See* AR (Vol. 27 Ref. 387).

[607] *Id.* at C1:39-41 (emphasis added).

U.S. Patent No. 3,280,823, Bayley A, Air B, Robb II EW, assigned to Philip Morris Inc., *Additive-Releasing Filter for Releasing Additives into Tobacco Smoke* (Oct. 25, 1966), at C1:43-45. *See* AR (Vol. 26 Ref. 352).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

b. RJR's Product Research and Development Efforts

RJR has also conducted product research and development to ensure that its cigarettes deliver levels of nicotine to smokers that provide desired pharmacological effects. A presentation from RJR's researchers to its marketing department in approximately 1977, for example, reveals that RJR understood the importance of maintaining adequate nicotine deliveries as tar deliveries declined and had identified a range of nicotine delivery levels capable of producing pharmacological effects. According to this presentation, nicotine has two roles in cigarettes. First, it contributes to the "mouth taste" or "mouth satisfaction" derived from a cigarette.[608] Second, and even more important, it "acts upon the central nervous system and produces in the average smoker a sensation one could describe as either stimulating or relaxing."[609] Moreover, according to the presentation, "a confirmed smoker attempts to get a certain desired level of nicotine. About one half hour after smoking, after all the nicotine has been biologically or pharmacologically inactivated, the smoker experiences a need for nicotine and lights up another cigarette."[610] For these reasons, the researchers reported that "a zero nicotine cigarette . . . really has no potential to provide smoking satisfaction. It produces no taste in the mouth, but even more seriously *it fails to provide the ultimate satisfaction in the lungs.*"[611]

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[608] Senkus M (R.J. Reynolds Tobacco Co.), *Some Effects of Smoking*, (1976/1977), at 7-9. *See* AR (Vol. 700 Ref. 593).

[609] *Id.* at 3.

[610] *Id.* at 5.

[611] *Id.* at 9 (emphasis added).

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The researchers observed that RJR's competitors "*are fully aware of the advisability of maintaining a low tar value and also maintaining the nicotine as high as possible.*"[612] They cited True, which is produced by Lorillard Tobacco Co., as an example of a cigarette in which tar levels had been reduced dramatically while nicotine levels had been left essentially unchanged, stating:

> [T]he old True had 11 mg tar [and] .6 mg nicotine -- the new True is 5 mg tar [and] .5 mg nicotine. So although the tar was reduced 6 mg from 11 mg to 5 mg, *nicotine was dropped only .1 mg. . . .*[613]

The researchers then recommended that RJR develop cigarettes that reduced tar but maintained nicotine at levels sufficient to provide "(1) mouth satisfaction—quality of nicotine" and "(2) ultimate physiological satisfaction—quantity of nicotine."[614] Specifically, RJR recommended that a new brand deliver 5 mg tar and 0.5 to 0.8 mg nicotine, stating that "*on inhalation into the lungs, 0.5 mg to 0.8 mg of nicotine would provide sufficient nicotine to the blood to produce the stimulation and relaxation effects desired by the smoker.*"[615] As discussed in section II.C.4.a.ii., below, RJR appears to have implemented these recommendations.

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Similar recommendations were made by Claude Teague, Jr., RJR's assistant director for research. As noted in section II.C.2.b.i., above, a 1972 memorandum written by RJR's assistant director for research, Charles Teague, referred to efforts at RJR to

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[612] *Id.* at 10 (emphasis added).

[613] *Id.* (emphasis added).

[614] *Id.* at 11.

[615] *Id.* at 11-12 (emphasis added).

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"reduc[e] the amount of 'tar' in cigarette smoke per unit of nicotine."[616] In its comments, RJR confirms that it has conducted research on cigarettes with enhanced nicotine-to-tar ratios.[617]

In addition to developing low-tar cigarettes that maintain adequate nicotine deliveries, RJR has been particularly active in developing novel tobacco products that deliver nicotine but few other components of tobacco smoke. As noted in section II.C.2.b.i., above, Teague first recommended such a "futuristic" product in 1972, urging that *"[t]here should be some simpler, 'cleaner', more efficient and direct way to provide the desired nicotine dosage than the present system involving combustion of tobacco."*[618]

RJR actually developed and marketed such an alternative tobacco product, called Premier, in the late 1980's. As described in section II.C.2.b.iii., above, RJR conducted comparative studies of the blood levels of nicotine produced by Premier and by conventional cigarettes to ensure that Premier delivered normal doses of nicotine to the user. However, because the tobacco in the product was heated rather than burned, it delivered the vapor recommended by Teague, with virtually no tar and other non-nicotine components of normal tobacco smoke.

Currently, RJR is test-marketing a similar product, "Eclipse." As described in section II.C.2.b.iii., above, Eclipse, like Premier, is intended to rely primarily on heating

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[616] Teague CE (R.J. Reynolds Tobacco Co.), *Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of Nicotine Therein* (Apr. 14, 1972), at 6 (emphasis added). *See* AR (Vol. 531 Ref. 125).

[617] R.J. Reynolds Tobacco Co., Comment (Jan. 2, 1996), at 3. *See* AR (Vol. 519 Ref. 103).

[618] Teague CE (R.J. Reynolds Tobacco Co.), *Research Planning Memorandum on The Nature of the Tobacco Business and the Crucial Role of Nicotine Therein* (Apr. 14, 1972), at 7 (emphasis added). *See* AR (Vol. 531 Ref. 125).

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rather than burning tobacco and to deliver levels of nicotine similar to a conventional ultra-low-tar cigarette, but much reduced levels of other cigarette smoke constituents.

RJR's extensive efforts to develop and market alternative cigarettes that deliver nicotine and little else show that it regards nicotine as the essential ingredient of tobacco. The efforts also show that RJR regards cigarettes as, in effect, devices for the delivery of nicotine.

Like Philip Morris, RJR also holds various patents on ways to manipulate nicotine deliveries, including patents intended to "provide a cigarette which delivers a larger amount of nicotine in the first few puffs than in the last few puffs"[619] and intended to mask the harsh flavor of cigarettes with increased levels of nicotine.[620] Regardless of whether the patents have been actually used in commercial cigarettes, they are further evidence of RJR's interest in developing ways to control and manipulate nicotine deliveries.

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c. Brown & Williamson's Product Research and Development Efforts

Like Philip Morris and RJR, Brown & Williamson and its parent BATCO have conducted research to identify the minimum and optimum doses of nicotine necessary to produce desired pharmacological effects and they have invested considerable resources to develop cigarettes that optimize the delivery of nicotine to smokers. In the case of Brown & Williamson and BATCO, these efforts have spanned over three decades and show a consistent focus on methods to maintain nicotine deliveries at levels sufficient to provide

[619] U.S. Patent No. 4,595,024, Greene TB, Townsend DE, Perfetti TA, assigned to R.J. Reynolds Tobacco Company, *Segmented Cigarette* (Jun. 17, 1986), at C2:23-26. *See* AR (Vol. 26 Ref. 370).

[620] U.S. Patent No. 4,830,028, Lawson JW, Bullings BR, Perfetti TA, assigned to R.J. Reynolds Tobacco Company, *Salts Provided from Nicotine and Organic Acid as Cigarette Additives* (May 16, 1989), at C1. *See* AR (Vol. 34 Ref. 593).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

pharmacological satisfaction while reducing tar deliveries. These product research and development efforts cover a wide variety of strategies to enhance nicotine deliveries, including the use of nicotine-rich tobacco blends, genetic manipulation of tobacco plants, chemical manipulation of tobacco blends, and novel filter designs.

i. Product Research and Development in the 1960's. BATCO's product research and development efforts to optimize nicotine delivery in the 1960's focused on three areas. According to an internal Brown & Williamson memorandum written in 1965, one goal of BATCO research was to "*find ways of obtaining maximum nicotine for minimum tar.*"[621] The approaches then under consideration for maximizing nicotine and minimizing tar included "alteration of blends," "addition of nicotine containing powders to tobacco," and "nicotine fortification of cigarette papers."[622] Similarly, at a 1967 BATCO conference, the researchers urged that "*[t]he development of low TPM, normal nicotine cigarettes should continue.*"[623]

As part of its effort in the 1960's to maximize nicotine while minimizing tar, BATCO investigated whether nicotine delivery could be controlled by increasing the proportion of "extractable nicotine" (also known as "free nicotine") in the smoke through increases in the alkalinity or pH of tobacco smoke. By changing the chemical characteristics of the smoke, this technique would increase the amount of nicotine

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[621] Griffith RB (Brown & Williamson), *Report to Executive Committee* (Jul. 1, 1965), at 2 (emphasis added). *See* AR (Vol. 27 Ref. 377).

[622] *Id.*

[623] Minutes of BATCO Group R&D Conference at Montreal, Canada (Oct. 25, 1967), at 4 (emphasis added). *See* AR (Vol. 27 Ref. 378-1). A "low TPM" cigarette refers to a cigarette low in "total particulate matter" or "tar."

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

absorbed by the smoker without raising the level of nicotine in the cigarette. A 1966 BATCO study confirmed that "the reaction of a smoker to the strength of the smoke from a cigarette could be correlated to *the amount of 'extractable' nicotine in the smoke, rather than to the total nicotine content.*" further explaining that "it would appear that the increased smoker response is associated with *nicotine reaching the brain more quickly.*"[624] A 1967 BATCO study found that the addition of PEI (polyethyleneimine) to filters caused a significant increase in the delivery of "extractable nicotine" to the smoker.[625] And a 1968 study reported a direct correlation between smoke pH and nicotine absorption in the mouth, stating that "*[n]icotine retention appears to be dependent principally on smoke pH and nicotine content.*"[626]

BATCO's second objective was to develop an alternative tobacco product that delivered nicotine but not tar. In the 1960's, BATCO's Charles Ellis worked on Project ARIEL, an early Premier-like tobacco product that involved heating rather than burning nicotine-enriched tobacco. According to a 1967 patent, "the invention . . . seeks primarily to furnish *a smoking device which will yield nicotine in an acceptable form, both psychologically and physiologically*, but without the necessity for taking into the system so much of the products of combustion as is usual when smoking a conventional

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[624] BATCO, *Further Work on 'Extractable' Nicotine* (Sep. 30,1966), at BW-W2-11617 (emphasis added). *See* AR (Vol. 62 Ref. 308).

[625] BATCO, *Retention between 'Extractable Nicotine' Content of Smoke and Panel Response* (Mar. 17, 1967), at 2. *See* AR (Vol. 176 Ref. 2045).

[626] BATCO, *The Retention of Nicotine and Phenols in the Human Mouth* (1968), at BW-W2-11691 (emphasis added). *See* AR (Vol. 445 Ref. 7593).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

cigarette."[627] Although ARIEL was never commercialized, Brown & Williamson continues to develop and patent similar tobacco products to this day.[628] Like RJR's development of Premier and Eclipse, Brown & Williamson and BATCO's development of these alternative tobacco products that deliver little more than nicotine shows that the companies regard cigarettes as, in effect, devices for the delivery of nicotine.

Third, BATCO launched efforts to find a nicotine analogue. A 1968 conference of BATCO researchers recommended:

> In view of its pre-eminent importance, the pharmacology of nicotine should continue to be kept under review and *attention paid to the possible discovery of other substances possessing the desired features of brain stimulation and stress-relief without direct effects on the circulatory system.*[629]

BATCO's interest in nicotine analogues led to a 1972 BATCO report that "concluded that substances closely related to nicotine in structure (nicotine analogues) could be important" because "[s]hould nicotine become less attractive to smokers, the future of the tobacco industry would become less secure."[630] Thus, as with Philip Morris,

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[627] U.S. Patent No. 3,356,094, Ellis CD, Dean C, Hughes IW, assigned to Battelle Memorial Institute, *Smoking Devices* (Dec. 5, 1967), at C2:66-71 (emphasis added). *See* AR (Vol. 34 Ref. 571).

[628] Philip Morris Inc., Draft Report Regarding a Proposal for a "Safer" Cigarette, Code-named *Table*, at 5 (stating that "[O]ther tobacco industry patent activity by . . . Brown & Williamson illustrates extensive interest in the development of a superior nicotine delivery device with or without a tobacco base"). *See* AR (Vol. 531 Ref. 122).

Slade J, Bero LA, Hanauer P, *et al.*, Nicotine and Addiction, the Brown & Williamson documents, *Journal of the American Medical Association* 1995;274(3):225-233, at 228. *See* AR (Vol. 528 Ref. 97).

[629] Minutes of BATCO Research Conference at Hilton Head, SC (Sep. 24-30, 1968), at 3 (emphasis added). *See* AR (Vol. 31 Ref. 525-1).

[630] Kilburn KD, Underwood JG (BATCO), *Preparation and Properties of Nicotine Analogues* (Nov. 9, 1972), at 1. *See* AR (Vol. 31 Ref. 524-1).

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Brown & Williamson's nicotine analogue research demonstrated the company's intention to preserve the effects of nicotine on the brain in new tobacco products.

Collectively, the three areas of product development research related to nicotine delivery in the 1960's show Brown & Williamson's long-standing focus on delivering pharmacologically active doses of nicotine to smokers.

ii. Product Research and Development to Maintain Pharmacologically Satisfying Doses of Nicotine while Lowering Tar. Documents in the administrative record indicate that BATCO's efforts in the 1970's coalesced around the objective of maintaining nicotine deliveries in lower-tar cigarettes. The minutes of a 1975 BATCO research conference, for instance, observed that "*[o]nce again the need for normal nicotine low tar cigarettes which appeal to the consumer was identified.*"[631] A year later, at a 1976 BATCO conference, the researchers predicted a "*clear opportunity*" for low-tar, normal-nicotine cigarettes "[p]rovided we can get smokers to dissociate tar from nicotine in their minds in terms of a possible health hazard."[632] At another 1976 conference, the researchers stated:

> [I]n that the 'benefits' of smoking appear to be related to nicotine, we can infer that the 'benefits' of smoking might disappear if cigarettes with low levels of nicotine became the norm . . .[633]

In conjunction with their efforts to develop cigarettes that were low in tar but maintained nicotine delivery, Brown & Williamson and BATCO conducted product

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[631] Minutes of BATCO Group R&D Conference at Merano, Italy (Apr. 2-8, 1975), at 4 (emphasis added). *See* AR (Vol. 27 Ref. 379-1).

[632] Minutes of BATCO Group R&D Conference on Smoking Behaviour at Southampton, England (Oct. 11-12, 1976), at 8. *See* AR (Vol. 27 Ref. 379-2).

[633] *Id.* at 4.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

development research in the 1970's and 1980's to determine the dose of nicotine required to produce satisfying pharmacological effects in smokers. Project Wheat was central to these efforts. The multiyear project had two parts. In Part 1, the attitudes of over 1,000 smokers were surveyed to assess their "inner need" to smoke.[634] In Part 2, the smokers were asked to assess experimental cigarettes with different nicotine deliveries.[635]

According to BATCO:

> The purpose of the survey was to classify smokers into a number of categories showing distinct patterns of motivation, and different levels of so-called Inner Need, as a first step towards testing the hypothesis that *a smoker's Inner Need level is related to his preferred nicotine delivery.*[636]

Project Wheat was thus designed to determine the optimum dose of nicotine delivered by cigarettes for individual smokers as a function of the strength of their "inner need" to smoke. BATCO researchers defined "inner need" as the smoker's use of cigarettes to relieve stress, aid concentration, control appetite, and relieve craving.[637] These are the characteristic pharmacological effects of nicotine. *See* section II.B., above. They also described "the 'inner need' dimension" as correlating "with the extent of inhalation, with *the craving for cigarettes when these are not available,* and with *the*

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[634] Wood DJ, Wilkes EB (BATCO), *Project Wheat - Part 1: Cluster Profiles of U.K. Male Smokers and their General Smoking Habits* (Jul. 10, 1975), at 1. *See* AR (Vol. 20 Ref. 204-1).

[635] Wood DJ (BATCO), *Project Wheat - Part 2: U.K. Male Smokers: Their Reactions to Cigarettes of Different Nicotine Delivery as Influenced by Inner Need* (Jan. 30, 1976). *See* AR (Vol. 20 Ref. 204-2).

[636] Wood DJ, Wilkes EB (BATCO), *Project Wheat - Part 1: Cluster Profiles of U.K. Male Smokers and their General Smoking Habits* (Jul. 10, 1975), at 1 (emphasis added). *See* AR (Vol. 20 Ref. 204-1).

[637] Wood DJ (BATCO), Project Wheat (Jan. 10, 1974). *See* AR (Vol. 177 Ref. 2056).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

difficulty which consumers anticipate in giving up smoking."[638] Thus, a nicotine level that satisfies "inner need" is one that provides desired pharmacological effects.

According to the BATCO researchers, the hypothesis that "inner need" is related to nicotine delivery should be "seen as part of a general approach to the problem of designing cigarettes of increased consumer acceptance."[639] They further explained: "*In considering which product features are important in terms of consumer acceptance, the nicotine delivery is one of the more obvious candidates. . . . The importance of nicotine hardly needs to be stressed, as it is so widely recognised.*"[640]

Project Wheat found that "[a]s predicted by the hypothesis, *High Need clusters tend to prefer relatively high nicotine cigarettes*, their optimum nicotine delivery being higher than that of Low Need clusters."[641] Project Wheat also found that there was a conflict between smokers' concern for health, which led them to favor low-tar brands of cigarettes, and their "inner need" to smoke, which led them to seek higher nicotine levels. According to the project report:

> Concern for the possible health risks of smoking influences consumers in the direction of trying low delivery brands. . . . However there is evidence of a conflict between concern for health and the desire for a satisfying cigarette, from which it follows that low tar brands would be much more widely accepted if their

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[638] *Regulation of Tobacco Products (Part 3): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 438 (Jun. 21 and 23, 1994) (emphasis added). *See* AR (Vol. 709 Ref. 3).

[639] Wood DJ, Wilkes EB (BATCO), *Project Wheat - Part 1: Cluster Profiles of U.K. Male Smokers and their General Smoking Habits* (Jul. 10, 1975), at 1. *See* AR (Vol. 20 Ref. 204-1).

[640] *Id.* at 3 (emphasis added).

[641] Wood DJ (BATCO), *Project Wheat - Part 2: U.K. Male Smokers: Their Reactions to Cigarettes of Different Nicotine Delivery as Influenced by Inner Need* (Jan. 30, 1976), at 1 (emphasis added). *See* AR (Vol. 20 Ref. 204-2).

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nicotine deliveries could be brought within the range required by groups of consumer[s]. [642]

Most important, the project developed a model of the cigarette market that showed a "substantial potential" for cigarettes that attract smokers concerned about both their health and satisfying their "inner need" for nicotine. According to the project report:

> *A model of the market is now proposed in which two major determinants of the type of cigarette which best suits a smoker's requirements are Inner Need and concern for health.* This model leads to the conclusion that *there is a substantial potential for a range of cigarettes which at present is not available. These cigarettes range from some with low tar and medium nicotine deliveries to others with medium tar and high nicotine deliveries,* and are visualised as attracting those smokers who combine above average Inner Need with above average concern for health.[643]

A chart in the Project Wheat report showed the magnitude of this new potential market. According to the chart, over 40% of smokers want a cigarette with lower tar and higher nicotine than currently available.[644]

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Project Wheat is persuasive evidence of the extensive product research and development by Brown & Williamson and BATCO to manipulate nicotine levels to provide pharmacologically active doses of nicotine. Project Wheat's "model of the market" showed the companies that there existed a significant market for cigarettes with low-tar levels but relatively enhanced nicotine levels.

Brown & Williamson and BATCO conducted additional research designed to correlate nicotine dose and pharmacological effects. For example, a 1980 BATCO Group

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[642] *Id.* at 48.

[643] *Id.* at 2 (emphasis added).

[644] *Id.* at 50-51.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

R&D report describes BATCO's successful effort to develop an improved method for measuring nicotine and its metabolites in the body. The method was developed to study the pharmacological effects of nicotine and their relationship to nicotine dose.

The report states that in some cases:

> the pharmacological response of smokers to nicotine is believed to be responsible for an individual's smoking behaviour, providing the motivation for and the degree of satisfaction required by the smoker.
>
> . . . .
>
> [W]here the causal relationship between nicotine and individual biochemical physiological or psychological responses are to be investigated, accurate information regarding nicotine dose is essential.[645]

A related study was designed to provide an animal model that would allow BATCO to estimate human nicotine doses and to aid in understanding the relationship between the dose of nicotine delivered by cigarettes and smokers' choice of particular brands.[646]

A session on "Nicotine Dose Estimation" at BATCO's 1984 Smoking Behaviour-Marketing Conference was intended "to review the current status of plasma/urinary measures . . . of nicotine dose and to identify the significance for the smoker and product design."[647] That same year, BATCO described its proposed research agenda for 1985-1987 as including studies "to establish the *minimum dose of smoke nicotine that can provide pharmacological satisfaction* for the smoker."[648]

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[645] Read GA, Anderson IGM (BATCO Group R&D), *Method for Nicotine and Cotinine in Blood and Urine* (May 21, 1980), at 2-3. *See* AR (Vol. 59 Ref. 235).

[646] Read GA, Anderson IGM, Chapman RE (BATCO Group R&D), *Nicotine Studies: A Second Report. Estimation of Whole Body Nicotine Dose by Urinary Nicotine and Cotinine Measurement* (Mar. 3, 1981), at 9-10. *See* AR (Vol. 59 Ref. 234).

[647] Proceedings of BATCO Group R&D Smoking Behaviour-Marketing Conference, Session II, Montreal, Canada (Jul. 9-12, 1984) (slide), at BW-WZ-02641. *See* AR (Vol. 23 Ref. 305).

[648] BATCO Group R&D Research Programme, 1984: Proposed revisions for 1985-87, Research Conference, Southampton, England (Sep. 1984), at 2 (emphasis added). *See* AR (Vol. 22 Ref. 280).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

As described below, Brown & Williamson and BATCO pursued three different strategies in the late 1970's and 1980's for reducing tar deliveries in cigarettes while maintaining adequate nicotine deliveries.

iii. Blending and "Y-1." One approach to reducing tar levels while maintaining adequate nicotine levels is through blending. As noted above in section II.C.3.c.i., BATCO researchers first investigated this approach 30 years ago, when they recommended "alteration of blends" as one way to obtain "maximum nicotine for minimum tar."[649] By 1976, they had concluded that "*there would appear to be a forthcoming demand for high nicotine tobaccos*" in view of the interest in increasing the nicotine/tar ratios in low tar cigarettes.[650]

By the late 1970's, Brown & Williamson had begun a decade-long effort to develop a high-nicotine flue-cured tobacco plant that came to be named "Y-1." As described in the Jurisdictional Analysis, the Agency found that the company used conventional and advanced genetic breeding techniques to develop a commercially viable plant that had almost twice the nicotine content of domestically grown varieties of flue cured tobacco. *See* 60 FR 41700-41702. Whereas typical domestic varieties of tobacco contain between 2.5% to 3.5% nicotine, Brown & Williamson's patent for Y-1 indicated that the company had succeeded in raising the nicotine level to about 6% by weight.[651] Brown & Williamson achieved this objective by cross-breeding commercial varieties of

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[649] Griffith RB (BATCO), *Report to Executive Committee* (Jul. 1, 1965), at 2. *See* AR (Vol. 27 Ref. 377).

[650] Minutes of BATCO Group R&D Conference on Smoking and Behaviour at Southampton, England (Oct. 11-12, 1976) at BW-W2-02311 (emphasis added). *See* AR (Vol. 27 Ref. 381).

[651] U.S. Patent application, Fisher PR, Hardison HA, Bravo JE. New Variety of Tobacco Plant, assigned to Brown & Williamson Tobacco Corp. (1991), at 1. *See* AR (Vol. 68 Ref. 14).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

tobacco with *Nicotiana rustica*, a wild tobacco variety that is very high in nicotine but is not used in commercial cigarettes because of its harshness.

Brown & Williamson had Y-1 made into a male sterile plant, a technique that ensures that when the plant is grown it will not produce seeds that can be appropriated by others.[652] Brown & Williamson grew the plant in Brazil.[653] The Agency further found, and the company does not dispute, that Y-1 was eventually used in five different brands of cigarettes in 1993, and that as of mid-1994 Brown & Williamson still had 3.5 million to 4 million pounds of additional Y-1 in storage.[654]

The purpose of Y-1 was to develop a high-nicotine tobacco that could be used as a "blending tool" so that products could be designed that were lower in tar but not lower in nicotine.[655] Although Brown & Williamson asserts that it never used Y-1 in commercial cigarettes to raise nicotine/tar ratios, the company does not dispute that its goal was to deliberately alter the traditional relationship between tar and nicotine. Indeed, Brown & Williamson implicitly concedes that the company used Y-1 to develop "prototypes" with increased nicotine/tar ratios and tested them on consumer panels.[656] The development of Y-1 thus provides direct evidence of Brown & Williamson's intention to enhance nicotine deliveries.

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[652] *Regulation of Tobacco Products (Part 3): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103 Cong., 2d Sess. 18 (Jun. 21, 1994) (testimony of David Kessler). *See* AR (Vol. 709 Ref. 3).

[653] *Id.* at 142 (testimony of Thomas Sandefur, chairman and CEO, Brown & Williamson).

[654] Transcript of FDA Meeting with Brown & Williamson (Jun. 17, 1994), at 124-125. *See* AR (Vol. 28 Ref. 414).

[655] *Id.* at 85-86.

[656] Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 32. *See* AR (Vol. 529 Ref. 104).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

iv. Chemical Manipulation. Another approach to reducing tar while maintaining adequate nicotine for the smoker is to alter the chemistry of tobacco smoke in a manner that increases the transfer of nicotine to the smoker. As discussed above, BATCO did work in this area in the 1960's, which suggested that increasing the percentage of "extractable nicotine" delivered to the smoker resulted in "nicotine reaching the brain more quickly."[657]

BATCO's research and development efforts continued in the 1970's and 1980's. In a 1976 research conference, BATCO researchers discussed how the use of a filter additive PEI or "alkali treatment" could "maintain normal nicotine reaction for the smoker while actually reducing the amount of nicotine per cigarette":

> A second approach . . . is to aim at a lower smoke production per cigarette (i.e. lower tar) while maintaining "normal" nicotine. Work along these lines is already going on. *A further modification of this approach is to maintain normal nicotine reaction for the smoker while actually reducing the total amount of nicotine per cigarette.* It is believed that this can be done, e.g. by the use of P.E.I. or by alkali treatment of tobacco stems. [658]

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Similar observations were made at other research conferences. In 1978, for instance, BATCO researchers stated: "With conventional cigarettes, the transfer of nicotine to the smoker from the tobacco has very low efficiency. Potentially, therefore, *opportunities exist for very big savings in tobacco if this low efficiency can be greatly increased.*"[659]

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[657] BATCO, *Further Work on 'Extractable' Nicotine* (1966), at BW-W2-11621. *See* AR (Vol. 62 Ref. 308).

[658] Memo: HA (BATCO), *Cigarettes with Health Reassurance* (1976), at 1 (emphasis added). *See* AR (Vol. 27 Ref. 380).

[659] Notes on BATCO Group R&D Conference at Sydney, Australia (Mar. 1978), at 4 (emphasis added). *See* AR (Vol. 26 Ref. 367).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

This would not be an "opportunity" if the company did not recognize that nicotine was the essential active ingredient intended to be delivered.

In 1982, BATCO researchers urged that a design objective for new products should be "to enhance or maximise sensory and pharmacological sensations, i.e., *'to make the smoke work harder'* so as to achieve maximum sensation at a given delivery level."[660] And in 1984, BATCO researchers discussed a study in which "*experimental cigarettes . . . will . . . be used to improve the efficient use of smoke nicotine through pH modification.*"[661]

v. "Elasticity" Technologies. A third approach to lowering tar while maintaining an adequate nicotine delivery is to increase the "elasticity" of cigarettes. "Elasticity" refers to the ability of a cigarette, whatever its nicotine yield as measured by a smoking machine, to deliver enough smoke to permit a smoker to obtain the nicotine the smoker needs. The elasticity of a cigarette can be increased, for instance, by placing ventilation holes in the filter. These holes allow fresh air to be pulled into the smoking machine during inhalation, thereby diluting the smoke and reducing the measured yields. However, the holes can be blocked by smokers' fingers or lips, allowing the smoker to obtain more nicotine than the machine measured delivery. *See* 60 FR 41716–41718. Brown & Williamson and BATCO sought to develop elasticity technologies. During a 1983 BATCO conference, BATCO researchers observed that "[e]lasticity can be designed

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[660] Minutes of BATCO Research Conference at Montebello, Canada (Aug. 30-Sep. 3, 1982), at 3 (emphasis added). *See* AR (Vol. 179 Ref. 2082).

[661] BATCO, *Proposed Revisions for 1985-1987* (Sep. 1984), at 1-2 (emphasis added). *See* AR (Vol. 26 Ref. 369-1).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

into a cigarette using tobacco blend and pressure drop components."[662] A year later, at a 1984 conference, BATCO researchers elaborated:

> Compensation by modifying smoking regime . . . is a topic which is being explored . . . and *this includes designing products which aid smoker compensation.*
>
> The marketing policy concerning this type of product is not clear but it is believed it will depend largely on the degree of elasticity in the design and how overtly this elasticity is achieved. *The consensus is that small improvements in elasticity which are less obvious, visually or otherwise is likely to be an acceptable route.*[663]

Taken together, Brown & Williamson and BATCO's product research and development efforts exhibit a sustained focus on nicotine over the course of three decades. The companies recognized through their research that significant marketing opportunities existed for cigarettes that reduced tar deliveries but maintained nicotine deliveries at levels high enough to satisfy smokers' "inner need" for nicotine. They then developed a broad range of techniques for enhancing nicotine deliveries. These extensive efforts are evidence of a "design" or "plan" to manipulate and control nicotine deliveries to provide a pharmacologically active dose of nicotine.

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d. Other Cigarette Manufacturers' Product Research and Development Efforts

i. American Tobacco Company. The American Tobacco Company (American Tobacco) also conducted extensive research and development on ways to increase and optimize nicotine deliveries. In 1969, for instance, the company

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[662] BATCO, *Smoking Behavior Conference: Overview* (1983), at BW-W2-03292. *See* AR (Vol. 27 Ref. 392).

[663] Proceedings of BATCO Group R&D Smoking Behaviour-Marketing Conference, Session III (Jul. 9-12, 1984), at 55 (emphasis added). *See* AR (Vol. 27 Ref. 391).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

manufactured Lucky Strike cigarettes enriched with a nicotine salt (nicotine malare) and sold them in the Seattle market.[664]

In 1974, the company's manager of new products, R. M. Irby, wrote to the vice president of manufacture and leaf, J. B. McCarthy, to summarize "our current knowledge regarding increasing the nicotine content of reconstituted tobacco."[665] Irby's memorandum stated that nicotine in reconstituted tobacco could be increased either by adding "Compound W," a code name for nicotine, to the reconstituted tobacco or by replacing "the lower nicotine-containing leaf components such as Turkish . . . with high nicotine tobacco such as Malawi sun-cured scrap (5% nicotine)."[666]

Three years later, American Tobacco researchers wrote a memorandum describing "suggested" ways of increasing the nicotine/tar ratio in cigarettes. The methods included the "addition of ammonia salts . . . to tobacco, which on smoking would free the ammonia and thereby cause an increase in nicotine transfer to the smoke."[667]

By 1980, American Tobacco was conducting experiments on this idea by adding a salt (potassium carbonate) to its Tareyton blend. According to the research memorandum describing the experiment, "[s]ince most nicotine in tobacco is a non-volatile salt, *it was*

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[664] Letter to Waxman HA, on behalf of the American Tobacco Company (Oct. 14, 1994), at 3. *See* AR (Vol. 26 Ref. 355).

[665] Irby RM Jr. (American Tobacco), *Nicotine Content of Reconstituted Tobacco* (Jun. 5, 1974), at 1. *See* AR (Vol. 26 Ref. 357-3).

[666] *Id.* at 1-2.

[667] Pederson PM (American Tobacco), *A Study of the Nicotine to Tar Ratio* (Apr. 18, 1977), at 4. *See* AR (Vol. 26 Ref. 365).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

thought that a greater transfer would take place if the tobacco was made basic causing the nicotine to volatilize when the cigarette is smoked." [668]

Other efforts by American Tobacco to increase the amount of nicotine delivered by its cigarettes are described in the Jurisdictional Analysis. *See* 60 FR 41675–41677. These efforts show that like Philip Morris, RJR, and Brown & Williamson, American Tobacco has designed and planned ways to enhance nicotine deliveries to smokers.

ii. Lorillard Tobacco Company. Like the other cigarette manufacturers, the Lorillard Tobacco Company developed knowledge about numerous ways to manipulate and control nicotine deliveries. For instance, in a 1975 presentation, Alexander Spears, the vice chairman and chief operating officer of Lorillard, stated that "[t]hrough [a] combination of . . . variables, . . . *it is possible to manipulate the yield of nicotine from about .1 mg to 4 mg per cigarette.*"[669] The variables cited by Spears as controlling nicotine deliveries included "the nicotine content of the tobacco"; "[the] porosity of the wrapper and/or ventilation at the filter"; "the affinity of the filter material for nicotine, particularly as a function of smoke pH"; and "plant genetics."[670]

In a 1981 paper on tobacco leaf blending, Spears further described "*the ways in which higher nicotine levels can be achieved.*"[671] Spears explained that nicotine

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[668] Bodenhamer NL (American Tobacco), *Leaf Services Monthly Report for June* (Jun. 30, 1980) (emphasis added). *See* AR (Vol. 27 Ref. 385)

[669] Spears AW (Lorillard Tobacco Co.), *Factors Affecting Smoke Delivery of Nicotine and Carbon Monoxide*, presented at the 1975 Symposium-Nicotine and Carbon Dioxide (Nov. 17-18, 1975), in Symposium Proceedings-1, at 13 (emphasis added). *See* AR (Vol. 27 Ref. 395a).

[670] *Id.*

[671] Spears AW, Jones ST (Lorillard Tobacco Co.), Chemical and Physical Criterias for Tobacco Leaf of Modern Day Cigarettes, *Recent Advances in Tobacco Science*, Oct. 6-9, 1981;7:19-39, at 23. *See* AR (Vol. 26 Ref. 373-1).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

concentrations of tobaccos vary widely, from 3.65% nicotine in upper-stalk Burley tobacco and 3.26% in upper-stalk flue-cured tobacco to 0.95% in Oriental tobacco and 0.85% in stem-sheet or reconstituted tobacco. According to Spears, "*[h]igher nicotine levels can be achieved* by decreasing Oriental and the stem and tobacco sheet and increasing the Burley and upper stalk positions of both the Flue-cured and the Burley tobacco."[672] He further observed that "*current research is directed toward increasing the nicotine levels* while maintaining or marginally reducing the 'tar' deliveries."[673]

The administrative record thus reveals that the cigarette manufacturers have consistently focused their product research and development efforts on developing methods to maintain or enhance nicotine deliveries. These activities are remarkable for their sustained duration and for the fact that each cigarette manufacturer independently acquired similar capabilities to manipulate and control nicotine deliveries. This again demonstrates the central role of nicotine delivery in the design of cigarettes.

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e. Filter and Paper Suppliers' Product Research and Development Efforts

The filter and paper suppliers for cigarette manufacturers also developed products to enhance nicotine deliveries, including methods for "increasing nicotine delivery *without* changing tar delivery[674] and for "alter[ing] cigarette nicotine delivery *independently* of tar

[672] *Id.* at 24 (emphasis added).

[673] *Id.* at 31 (emphasis added).

[674] Selke WA. Making the cigarette do just what you want it to do. *Journal Tobacco International*, 1983:12 (emphasis added). *See* AR (Vol. 102 Ref. 896).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

delivery."[675] These efforts are not direct evidence of the manufacturers' intent, because the product development was conducted by suppliers, rather than the manufacturers themselves. Nevertheless, the suppliers' efforts corroborate the Agency's finding that the cigarette manufacturers seek the capability to enhance nicotine deliveries in low-tar cigarettes. They show that the suppliers understood manufacturers to be interested in acquiring products that would enable the manufacturers to selectively remove more tar than nicotine from cigarette smoke.

To develop products with enhanced nicotine deliveries, the filter and paper suppliers altered the filtration and ventilation systems in cigarettes. Filters are used to trap smoke particles before they enter the mouths of smokers. Ventilation technologies draw air into the cigarette through holes in the filter or through porous cigarette paper, diluting the smoke. The suppliers found that these systems could be manipulated to selectively remove more tar than nicotine, thereby increasing the nicotine/tar ratio in the smoke.

Documents in the administrative record describe several of the methods developed for increasing nicotine delivery relative to tar. According to one report, "[s]imply changing the location of the vents in a . . . filter has a measurable effect on the cigarette performance," with "the nicotine content [being]. . . greatest when the vents were positioned where the tobacco and filter were joined."[676] The same effect could be achieved by perforating the cigarette paper. One report found that "[i]ncreasingly porous

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[675] Lee BM (Eastman Kodak Company), *Modification of Nicotine to Tar Ratio in Cigarette Smoke*, 42nd Tobacco Chemists' Research Conference, Lexington, Kentucky (Oct. 2-5, 1988), at 33 (emphasis added). *See* AR (Vol. 639 Ref. 2).

[676] Kiefer JE, Ventilated Filters and Their Effect on Smoke Composition, *Recent Advances in Tobacco Science* (1979), at 79. *See* AR (Vol. 28 Ref. 465).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

perforated papers . . . *selectively increase nicotine*. . . ."[677] Research by a tobacco company confirmed the influence of paper design on tar and nicotine deliveries, finding that "tar/nicotine ratios are determined primarily by paper permeability; high permeability produces the lowest tar/nicotine ratios."[678] A low tar/nicotine ratio is mathematically equivalent to a high nicotine/tar ratio.

Other reports have shown that cigarettes designed with increased ventilation and less filtration will "increas[e] nicotine delivery without changing tar delivery;"[679] and that the use of additives to increase the pH of the filter will alter cigarette nicotine delivery independently of tar delivery, increasing the nicotine/tar ratio by up to 15%.[680]

f. These Product Research and Development Efforts Were Undertaken for Commercial Reasons

The cigarette manufacturers do not generally dispute that they engaged in the product research and development activities described above. Instead, they argue that their research on increasing or maintaining nicotine delivery while lowering tar was largely in response to "government" initiatives. In support of this claim, these comments refer to

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[677] Owens Jr. WF (Ecusta Paper and Film Group), *Effect of Cigarette Paper on Smoke Yield and Composition*, 32d Tobacco Chemists' Research Conference, Montreal, Canada (1978) (emphasis added). *See* AR (Vol. 639 Ref. 2).

[678] McMurtrie A, Litzinger EP, and Wu DT, *Cigarette Paper Effects on Tar/Nicotine and CO/Tar Ratios*. 35th Tobacco Chemists' Research Conference, Winston-Salem, North Carolina (1981). *See* AR (Vol. 639 Ref. 2).

[679] Selke WA, Making the cigarette do just what you want it to do, *Journal Tobacco International* 1983:12. *See* AR (Vol. 102 Ref. 896).

Browne CL (Brown & Williamson), *The Design of Cigarettes*, at 72. *See* AR (Vol. 27 Ref. 399).

[680] Lee BM (Eastman Kodak Company), *Modification of Nicotine to Tar Ratio in Cigarette Smoke*, 42nd Tobacco Chemists' Research Conference, Lexington, Kentucky (Oct. 2-5, 1988), at 33. *See* AR (Vol. 639 Ref. 2).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

a few sentences in a 1981 report of the U.S. Surgeon General, the recommendation of a scientist at NIH in 1976, and a few scattered articles from nongovernment researchers beginning in 1973. The comments offer no evidence from company documents to show that any part of the industry's extensive research on increasing nicotine delivery from low-tar cigarettes was actually motivated by the cited "initiatives."

The evidence in the administrative record also fails to support the industry's claims. The large number of internal tobacco company documents available to FDA indicates that the companies' product research and development was conducted for commercial reasons. Philip Morris, for instance, stated that "the rationale" for its research and development efforts "rests on the premise that such knowledge will strengthen Philip Morris R&D capability in developing new and improved smoking products."[681]

The driving force behind the efforts to enhance nicotine delivery in low-tar products was the industry's knowledge that people use tobacco for nicotine and that below a certain nicotine level, the motivation for tobacco use, and the market for tobacco products will disappear. RJR researchers knew in the 1970's that "a zero nicotine cigarette . . . fails to provide the ultimate satisfaction in the lungs;" hence they recommended "*maintaining the nicotine as high as possible*" in low-tar cigarettes.[682] Similarly, a 1976 BATCO "Smoking Behaviour" conference report shows that BATCO was aware of the need to maintain adequate nicotine deliveries, stating that "the 'benefits' of smoking appear to be related to nicotine, [and] we can infer that the 'benefits' of

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[681] Dunn WL, *Plans and Objectives--1979* (Dec. 6, 1978), in 141 Cong. Rec. H7669 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[682] Senkus M (R.J. Reynolds Tobacco Co.), *Some Effects of Smoking* (1976/1977), at 9, 10 (emphasis added). *See* AR (Vol. 700 Ref. 593).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

smoking might disappear if cigarettes with low levels of nicotine became the norm."[683] Likewise, a 1972 Philip Morris presentation indicates that Philip Morris knew that cigarettes with inadequate levels of nicotine would not be purchased by smokers.[684]

Moreover, the industry's research on selectively increasing or maintaining nicotine while lowering tar cannot be attributed to government initiatives because it began before the earliest government "initiative" cited by the comments. For example, as noted in section II.C.3.c.i. above, Brown & Williamson was developing "ways of obtaining maximum nicotine for minimum tar" at least as early as 1965[685]—well before the 1976 NIH and the 1981 Surgeon's General documents cited by the industry. Similarly, Philip Morris was working on increasing nicotine levels in relation to tar as early as 1970, when it began experimentally altering the nicotine/tar ratio of Marlboro cigarettes by "reduc[ing] the tar delivery incrementally . . . and increas[ing] the nicotine delivery incrementally by adding a nicotine salt."[686] Thus, the industry was plainly developing low-tar, enhanced-nicotine products before any of the cited "government initiatives."

Finally, FDA notes that to the extent that the industry accepted the recommendations of outside researchers who suggested the development of low-tar, high-nicotine products, those recommendations were based on the researchers' conclusion that

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[683] Minutes of BATCO Group R&D Conference on Smoking and Behaviour at Southampton, England (Oct. 11-12, 1976), at 4. *See* AR (Vol. 27 Ref. 376).

[684] Dunn WL (Philip Morris Inc.), *Motives and Incentives in Cigarette Smoking* (1972), at 4 (emphasis added). *See* AR (Vol. 12 Ref. 133).

[685] Griffith RS (BATCO), *Report to Executive Committee* (Jul. 1, 1965), at 2. *See* AR (Vol. 27 Ref. 377).

[686] Eichorn PA, Dunn WL (Philip Morris Inc.), *Quarterly Report of Projects 1600 and 2302–Oct. 1-Dec. 31, 1970* (Dec. 31, 1970), in 141 Cong. Rec. H8128 (daily ed. Aug. 1, 1995). *See* AR (Vol. 27 Ref. 376).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

smokers seek adequate doses of nicotine to satisfy dependence and will compensate to achieve those doses when given a low-nicotine cigarette.[687] The cigarette industry, in contrast, denies that smokers compensate for nicotine to any significant extent. It is not credible that the industry would have accepted and acted on outsiders' recommendations while rejecting the fundamental premises on which the recommendations were based. Moreover, the Surgeon General, while suggesting that cigarettes with a lower tar-to-nicotine ratio should be investigated, specifically cautioned against achieving this goal through strategies that reduced tar while maintaining a normal nicotine yield:

> [F]actors of "smoker compensation" must be considered in the evaluation of lower "tar" and nicotine cigarettes. Filtered, lower "tar" and nicotine cigarettes that are less vulnerable to increasing the smoke and nicotine deliveries are needed. . . . Attempting to minimize smoker compensation by selectively reducing "tar" and other smoke compounds while maintaining nicotine yield may carry serious disadvantages. First, maintaining nicotine delivery may reinforce physiologic habituation, and interfere with smoking cessation attempts. Second, nicotine gives rise to the tobacco-specific carcinogenic N-nitrosamines . . . Finally, nicotine is suspected to be a major smoke constituent correlated with the increased risk of cardiovascular disease among cigarette smokers.[688]

Accordingly, the evidence establishes that the industry researched and developed methods to increase relative nicotine deliveries while decreasing tar deliveries for a commercial purpose—to ensure that cigarettes provide pharmacologically satisfying doses of nicotine.

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[687] *See, e.g.*, Russell MAH, *et al.*, Comparison of effect on tobacco consumption and carbon monoxide absorption of changing to high and low nicotine cigarettes, *British Medical Journal* 1973;4:512-516. *See* AR (Vol. 89 Ref. 485).

Gori G. Low risk cigarettes: a prescription, *Science* 1976;94(4271):1243-1246. *See* AR (Vol. 535 Ref. 96, vol. IV.D, at 1-5).

[688] Department of Health and Human Services, *The Health Consequences of Smoking: The Changing Cigarette, A Report of the Surgeon General, 1981*, at 98 (citation omitted). *See* AR (Vol. 123 Ref. 1586).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

4. The Cigarette Manufacturers Design Commercially Marketed Cigarettes to Provide a Pharmacologically Active Dose of Nicotine

The evidence summarized in section II.C.3. that the manufacturers have conducted product research and development to establish the doses of nicotine needed to produce pharmacological effects and to optimize nicotine deliveries to consumers establishes that the manufacturers have the capacity to design cigarettes that provide pharmacologically active doses of nicotine. In this section, the Agency evaluates the evidence in the record regarding the manipulation and control of nicotine in commercial cigarettes.[689]

As discussed below, the evidence in the administrative record establishes that many of the product research and development efforts described in section II.C.3. are used in important ways in the commercial cigarettes marketed today. The available evidence shows that the cigarette manufacturers pay careful attention to nicotine in all phases of cigarette manufacture. As described in the Jurisdictional Analysis, the focus on nicotine is apparent at each step—from the growing and purchasing of tobacco leaves, to the blending of different tobacco varieties, to the design and manufacture of the finished cigarette. *See* 60 FR 41693–41733.

The evidence in the record further demonstrates that the final products—the finished cigarettes sold to consumers—reflect the manufacturers' careful attention to

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[689] The evidence in section II.C.2., supported by the evidence in section II.C.3. that the manufacturers "have in mind" that these products will have and be used for pharmacological effects, is sufficient by itself to establish intended pharmacological use. It is thus not necessary for the Agency to establish that commercial cigarettes have been affirmatively designed to provide a pharmacologically active dose of nicotine to show that the manufacturers "intend" the pharmacological effects and uses of cigarettes. For example, a manufacturer of a traditional full-strength cigarette may not need to take any specific design steps to insure that the cigarette provides a pharmacologically active dose of nicotine. Nevertheless, this manufacturer's understanding and expectation that the full-strength cigarette will be used by consumers for drug purposes would be sufficient to establish the cigarette's intended pharmacological use.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

nicotine. Manufacturers of commercially marketed cigarettes commonly manipulate nicotine deliveries to provide remarkably precise, pharmacologically active doses of nicotine to consumers. The principal techniques that are used to control and manipulate nicotine deliveries include: (1) the use of nicotine-rich tobacco blends in low-tar cigarettes; (2) the use of filtration and ventilation technologies that selectively remove more tar from smoke than nicotine; and (3) the use of chemical additives that increase the percentage of "free" nicotine in cigarette smoke. Control is also achieved as a result of extensive attention to nicotine in tobacco breeding, leaf purchasing, leaf blending, and the manufacture of reconstituted tobacco.

Indeed, the evidence in the record establishes that cigarette designs in recent decades have been driven by the manufacturers' desire to maintain nicotine deliveries at pharmacologically active levels. As consumer awareness of the health effects of smoking has increased, the cigarette manufacturers have responded by adding filters and using ventilation to reduce tar deliveries. However, the manufacturers have not reduced nicotine deliveries proportionately. Rather, the evidence available to the Agency indicates that they have strived to ensure that nicotine deliveries remain at a pharmacologically active level.[690]

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a. The Manufacturers Use Nicotine-Rich Tobacco Blends in Low-Tar Cigarettes

Perhaps the clearest example of deliberate manipulation and control to maintain nicotine deliveries at levels sufficient to provide pharmacological satisfaction occurs in the

[690] RJR's Eclipse, the new tobacco product that is being test-marketed, carries this effort to close to its logical conclusion—maintaining nicotine deliveries at the level of conventional ultra-low-tar cigarettes while allegedly reducing many of the tar components of tobacco smoke substantially below these levels. Eclipse is discussed further in section II.C.3.b., above (product research and development).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

manufacture of low-tar cigarettes. The evidence in the administrative record indicates that cigarette manufacturers commonly use nicotine-rich tobacco blends in these products. Approximately 80% of the cigarettes on the market today are either low-tar (6 to 15 mg tar) or ultra-low-tar (less than 6 mg tar).[691]

i. The Use of Nicotine-Rich Tobacco Blends in the 1950's. The evidence in the record indicates that the use of richer nicotine blends first occurred in the 1950's, when filters were first added to cigarettes. Documents provided to the Agency by the tobacco industry show that a shift to higher nicotine blends occurred to offset the reductions in nicotine deliveries caused by the use of filters. According to one 1956 document: "*With the increase in production of filter tip cigarettes, . . . demand has increased for heavier-bodied [tobacco] types that have* full aroma and flavor and *a relatively high nicotine content.*"[692]

As early as 1957, the U.S. Department of Agriculture (USDA) recognized that the introduction of filters was causing increased demand for higher nicotine tobacco. That year, the director of the tobacco division of USDA's Agricultural Marketing Service, Stephen E. Wrather, testified before Congress that the industry had "moved up the stalk"

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[691] Federal Trade Commission, *Report of "Tar," Nicotine, and Carbon Monoxide of the Smoke of 1107 Varieties of Domestic Cigarettes* (1995). *See* AR (Vol. 535 Ref. 96, vol. IV.B).

[692] Jones GL, Collins WK, *Measured Crop Performance Tobacco 1956*, Department of Field Crops, N.C. State College, Raleigh N.C., Research Report No. 4 (Dec. 1956), at 1 (emphasis added). *See* AR (Vol. 535 Ref. 96, vol. IV.K).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

in blending tobacco for use in filter cigarettes.[693] "Moving up the stalk" is a reference to the higher nicotine content in the upper leaves of tobacco plants.[694]

Wrather also indicated that using this higher nicotine tobacco in the blend for filtered cigarettes enabled manufacturers to maintain the same "strength" levels in the smoke that existed in unfiltered cigarettes.[695] A 1957 *Consumer Reports* analysis of nicotine levels in filtered and unfiltered cigarettes placed in the record of the hearing showed that the average nicotine content in regular-size cigarettes with filters was higher than in regular-size cigarettes without filters.[696] This could only have been accomplished through the use of higher nicotine tobacco leaves in the blend for filtered cigarettes.

ii. The Use of Nicotine-Rich Tobacco Blends Today. During the 1960's and 1970's, the demand of consumers for "healthier" cigarettes led to further declines in tar yields. As described above in section II.C.3., this caused the cigarette manufacturers to develop methods to ensure that the nicotine levels in cigarettes did not drop below acceptable levels.[697]

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[693] *False and Misleading Advertising (Filter-tip Cigarettes): Hearings Before the Subcommittee of the Committee on Government Operations, U.S. House of Representatives*, 85th Cong., 1st Sess. 189 (1957) (testimony of Stephen E. Wrather). *See* AR (Vol. 172, Ref. 2035).

[694] *See, e.g.*, Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 10 ("Higher stalk tobacco leaves do have more nicotine than lower stalk leaves on the same plant"). *See* AR (Vol. 529 Ref. 104).

[695] *False and Misleading Advertising (Filter-tip Cigarettes): Hearings Before the Subcommittee of the Committee on Government Operations, U.S. House of Representatives*, 85th Cong., 1st Sess. 196 (1957) (testimony of Stephen E. Wrather). *See* AR (Vol. 172, Ref. 2035).

[696] *Id.* at 662 (exhibit 15c).

[697] Philip Morris USA, Research and Development Five Year Plan, 1974-1978 (May 1973), in 141 Cong. Rec. H8130-8131 (daily ed. Aug. 1, 1995). *See* AR (Vol. 711 Ref. 6).

See also Low Delivery Cigarettes and Increased Nicotine/Tar Ratios, A Replication (Oct. 1975), in 141 Cong. Rec. H8009 (daily ed. Jul. 31, 1995). *See* AR (Vol. 27 Ref. 376a).

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The evidence in the record indicates that the low-tar cigarettes on the market today reflect the industry's concerns with providing an acceptable nicotine level. As numerous documents in the record reveal, low-tar cigarettes are specifically blended to increase their nicotine concentrations. For instance, the administrative record includes the following descriptions of the use of blending to control and manipulate nicotine:

- William Farone, the former director of applied research at Philip Morris, stated that "[t]he industry employs two principal means of controlling the nicotine levels."[698] One of these is "*modification and control of the tobacco blend*, i.e., the ratio of Burley (air-cured), Bright (flue-cured), Oriental, stems, expanded tobacco products, and reprocessed tobacco products such as tobacco sheet made from stems and waste leaf."[699] According to Farone:

> *Product developers and blend and leaf specialists were responsible for manipulating and controlling the design and production of cigarettes in order to satisfy the consumer's need for nicotine in lower yield products.*
>
> *Blend changes were an especially important tool used to ensure desired nicotine levels.* Tar is a function of tobacco weight. However, an all-burley cigarette will produce a higher nicotine level than an all-bright cigarette of the same weight. The industry knew that by using a higher percentage of higher nicotine tobacco in their low tar cigarettes they could achieve an increase of their nicotine levels.[700]

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Jones B, Houck W, Martin P (Philip Morris Inc.), *Low Delivery Cigarettes and Increased Nicotine/Tar Ratios. A Replication* (Oct. 1975), in 141 Cong. Rec. H8132 (daily ed. Aug. 1, 1995). *See* AR (Vol. 711 Ref. 6).

Wood DJ, Wilkes EB (BATCO), *Project Wheat - Part 2: U.K. Male Smokers: Their Reactions to Cigarettes of Different Nicotine Delivery as Influenced by Inner Need* (Jan. 30, 1976), at 2. *See* AR (Vol. 20 Ref. 204-2).

[698] Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 5. *See* AR (Vol. 638 Ref. 2).

[699] *Id.* at 5 (emphasis added).

[700] *Id.* at 10 (emphasis added).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

- Ian Uydess, the former Philip Morris scientist, stated that:

> Nicotine levels were routinely targeted and adjusted by Philip Morris in its various products at least in part, through blend changes . . . .
>
> . . . .
>
> When Philip Morris designed a new or modified blend, they used their stored tobacco inventories much like a scientist would use a chemical stockroom to select the ingredients needed to synthesize a new material. . . .
>
> . . . *Philip Morris routinely applied this knowledge of selective tobacco blending to achieve desired nicotine . . . levels in the products that it designed and marketed.*[701]

- Alexander Spears, the vice chairman and chief operating officer of Lorillard Tobacco Co., wrote that "*the lowest 'tar' segment is composed of cigarettes utilizing a tobacco blend which is significantly higher in nicotine.*"[702] According to Spears, the nicotine concentration in the lowest tar cigarettes in 1981 was 22% greater than the concentration in regular cigarettes (2.2% versus 1.8%).[703] Spears further explains that "[h]igher nicotine levels can be achieved by decreasing Oriental and the stem and tobacco sheet and increasing the Burley and upper stalk positions of both the flue-cured and the Burley tobacco."[704]

- Another Lorillard researcher, Vello Norman, has explained that the shift to tobacco blends with more nicotine-rich burley tobacco was motivated by a desire "to impart

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[701] Declaration of Uydess IL (Feb. 29, 1996), at 8, 10 (emphasis added). *See* AR (Vol. 638 Ref. 1).

[702] Spears AW, Jones ST (Lorillard Tobacco Co.), Chemical and Physical Criteria for Tobacco Leaf of Modern Day Cigarettes, *Recent Advances in Tobacco Science*, Oct. 6-9, 1981;7:19, at 22 (emphasis added). *See* AR (Vol. 26 Ref. 373).

[703] *Id.* at 21.

[704] *Id.* at 24.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

more impact to smoke" to offset the effects of "gradually lower cigarette smoke yields":

> As various means were used to gradually lower cigarette smoke yields there has been a tendency to use more Burley in order to impart more impact to smoke. Thus, while total smoke yields of cigarettes have diminished, the relative composition of smoke has, in the case of many cigarettes, shifted slightly towards what is more characteristic of Burley.[705]

"Impact" is a term used by the tobacco industry to describe effects that are associated with nicotine delivery. *See, e.g.*, Jurisdictional Analysis, 60 FR 41776–41777.

- Similarly, a scientist at Brown & Williamson reported that "*[u]ltra low tar cigarettes . . . use blends which contain about 20% more nicotine.*"[706]

Brown & Williamson's development of the high-nicotine Y-1 variety of tobacco, which is discussed above in section II.C.3.c.iii., was an attempt to use breeding and blending to increase nicotine concentrations in low-tar cigarettes. An example in which blending has been used to increase nicotine concentrations in commercial low-tar cigarettes is Philip Morris' Merit cigarettes. FDA has analyzed the relative nicotine concentrations in the regular, low-tar, and ultra-low-tar versions of Merit cigarettes. FDA's analysis revealed that Merit Filter 100's contained 1.46% nicotine, but that Merit Ultra Lights 100's contained 1.67% nicotine, and Merit Ultima 100's (the lowest-tar product) contained 1.99% nicotine. *See* 60 FR 41723–41724. These findings, which

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[705] Norman V (Lorillard Research Center), *Changes in Smoke Chemistry of Modern Day Cigarettes*, Greensboro, NC (1982), at 168. *See* AR (Vol. 99 Ref. 813).

[706] Reynolds ML (Brown & Williamson), *Symposium Summary*, presented at Winston Salem, NC, at 179 (Oct. 6-9, 1981) (emphasis added). *See* AR (Vol. 99 Ref. 823).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

show nicotine concentrations increasing as reported tar yields drop, are unchallenged by Philip Morris.

A similar pattern of higher nicotine concentrations in lower tar products exists in other brands. For instance, in 1981, Brown & Williamson launched a new ultra-low-tar brand called Barclay. Tests of Barclay and fourteen other cigarettes in 1982 showed that the tobacco in the Barclay blend had a nicotine concentration of 2.69%—higher than any other brand tested. In fact, Barclay's nicotine concentration was over 90% higher than the regular-strength Lucky Strike cigarette tested.[707] Other brands show the same pattern of higher nicotine concentrations in the lowest-tar cigarettes.

These industry blending practices facilitate the use of low-tar products for pharmaceutical purposes. The enhanced nicotine concentrations in the lowest tar cigarettes result in higher nicotine deliveries than would otherwise occur, allowing consumers to more readily satisfy their addiction to nicotine and obtain other pharmacological effects of nicotine from low-tar cigarettes.

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iii. The Use of Nicotine-Rich Tobacco Blends Is Not Due to Accident or Taste. In the Jurisdictional Analysis, FDA summarized the evidence then available to the Agency regarding the use of nicotine-rich blends in low-tar cigarettes, concluding that "[s]ignificant evidence also demonstrates that tobacco manufacturers have used blending techniques to increase nicotine concentrations in low-tar cigarettes and thereby maintain nicotine delivery while reducing tar delivery." 60 FR 41708. The public comment period

[707] *Regulation of Tobacco Products (Part 3): Hearings Before the Subcommittee on Health and the Environment, House Energy and Commerce Committee, U.S. House of Representatives*, 103d Cong., 2d Sess. 173 (Jun. 23, 1994). *See* AR (Vol. 709 Ref. 3).

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provided the cigarette manufacturers with an opportunity to provide an alternative explanation of this evidence of nicotine manipulation. As explained below, however, the industry does not effectively rebut the evidence that the manufacturers use nicotine-rich blends to enhance nicotine deliveries. The industry's failure to provide a convincing counter-explanation for its actions is further support for the Agency's finding that the manufacturers design low-tar cigarettes with nicotine-rich blends to maintain adequate nicotine deliveries.

The cigarette manufacturers make two conflicting arguments in response to the evidence that they manipulate tobacco blends to enhance nicotine content in low-tar products. First, they categorically assert that they "do not independently 'control' for or 'manipulate' the nicotine content in any of their blends."[708]

Second, they maintain that, to the extent they do control and manipulate nicotine content, they do so strictly for taste. Thus, they contend that (1) they "blend their tobaccos for flavor"[709] and (2) "nicotine plays an important role in the taste and flavor of cigarette smoke."[710] During his appearance before Congress, for instance, William Campbell, the president of Philip Morris, conceded that the ultra-light Merit Ultima cigarette uses a tobacco blend with a higher concentration of nicotine than the regular Merit cigarette, but insisted that "it's there for taste."[711] Similarly, Thomas Sandefur, then

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[708] Joint Comment of Cigarette Manufacturers (Jan. 2, 1996), Vol. IV, at 66. *See* AR (Vol. 535 Ref. 96).

[709] *Id.*

[710] R.J. Reynolds Tobacco Co., Comment (Jan. 2, 1996), at 50. *See* AR (Vol. 519 Ref. 103).

[711] *Regulation of Tobacco Products (Part 1): Hearings Before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 764 (Apr. 14, 1994) (testimony of W.I. Campbell). *See* AR (Vol. 707 Ref. 1).

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CEO of Brown & Williamson, conceded under questioning that Brown & Williamson uses high-nicotine blends in low-tar products, but asserted that "*[w]hat we were trying to do was maintain a certain amount of nicotine which gives us better taste.*"[712]

Based on the evidence in the record, the Agency finds the manufacturers' contention that they do not control and manipulate nicotine levels in blends not to be credible. The high nicotine content in the blends of low-tar cigarettes is not an accident. It necessarily reflects the deliberate design choices of the manufacturers. Moreover, the manufacturers' argument that they do not control and manipulate the nicotine content of blends is in fundamental conflict with their assertions that they manipulate nicotine for taste.

For several reasons, the Agency also does not regard the manufacturers' assertion that they control and manipulate nicotine only for taste to be credible. First, the manufacturers' assertion is contradicted by numerous internal statements of senior researchers and officials in the tobacco industry, made public during the Agency's investigation. As discussed above in section II.C.2., many senior researchers and officials within the industry explicitly acknowledge that nicotine provides desired pharmacological effects to consumers, and refer to cigarettes as a "dispenser for a dose unit of nicotine,"[713] a "nicotine delivery device,"[714] "a vehicle for delivery of nicotine,"[715] "the means of

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[712] *Regulation of Tobacco Products (Part 3): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Congress, 2d Sess. 227 (Jun. 23, 1994) (statement of Thomas Sandefur) (emphasis added). *See* AR (Vol. 709 Ref. 3).

[713] Dunn WL (Philip Morris Inc.), *Motives and Incentives in Cigarette Smoking* (1972), at 5. *See* AR (Vol. 12 Ref. 133).

[714] Philip Morris Inc., Draft Report Regarding a Proposal for a "Safer" Cigarette, Code-named *Table*, at 5. *See* AR (Vol. 531 Ref. 122).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

providing nicotine dose in a metered fashion,"[716] and a device that provides the smoker "very flexible control over titrating his desired dose of nicotine."[717] Other senior executives have stated that the cigarette industry is "in the business of selling nicotine, an addictive drug . . ."[718] and that "a good part of the tobacco industry is concerned with the administration of nicotine to consumers."[719] The industry's argument that high-nicotine blends are used in cigarettes only for taste cannot be reconciled with the industry's own internal statements that cigarettes are intended to deliver pharmacological doses of nicotine to consumers. Indeed, one Philip Morris document quoted by the company in its comments calls nicotine a "*tasteless*" constituent of tobacco.[720]

Second, the manufacturers' position on nicotine and taste cannot be reconciled with the industry's record of extensive research into nicotine pharmacology. In contrast, very little of the industry's research has examined the role of nicotine in taste. In their comments the cigarette manufacturers cite only a handful of industry studies on this subject. FDA has reviewed all of these studies and finds that they do not substantiate the industry's claim that nicotine's effects on taste are the reason consumers smoke. *See*

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[715] Teague, CE (R.J. Reynolds Tobacco Co.), *Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of Nicotine Therein* (Apr. 14, 1972), at 1. *See* AR (Vol. 531 Ref. 125).

[716] Proceedings of the BATCO Group R&D Smoking Behaviour-Marketing Conference, Session I, slides (Jul. 9-12, 1984), at BW-W2-03242. *See* AR (Vol. 24 Ref. 315).

[717] *Transdermal Nicotine Patches*, at 2. *See* AR (Vol. 531 Ref. 124).

[718] Yeaman A (Brown & Williamson), *Implications of Battelle Hippo I and II and the Griffith Filter* (Jul. 17, 1963), at 4. *See* AR (Vol. 21 Ref. 221).

[719] Green SJ (BATCO), *BAT Group Research* (Sep. 4, 1968), at 2. *See* AR (Vol. 15 Ref. 192).

[720] Philip Morris Inc., Comment (Apr. 19, 1996), at 64-65 (emphasis added), citing, "Merit Team Second Speaker" (Jan. 14, 1976). *See* AR (Vol. 700 Ref. 226).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

section II.B.2.c., above. Philip Morris's comments do state that Philip Morris conducted sophisticated investigations into flavor using an EEG-assisted "olfactometer." Yet according to Philip Morris, "*[n]one of that 'olfactometer' work involved nicotine at all*"[721]—an omission that conflicts with the industry's assertion that nicotine has an important role in flavor.

By contrast, the industry has conducted or funded hundreds of studies on nicotine pharmacology, focused primarily on nicotine's effects on brain function. Manufacturers have learned through this research that nicotine has the hallmark characteristics of an addictive drug, *see* section II.C.3., above, and "abuse liability",[722] that nicotine changes patterns of human brain waves in a manner associated with anxiety relief;[723] and that "[n]icotine is an extremely biologically active compound capable of eliciting a range of pharmacological, biochemical and physiological responses."[724]

The research conducted by several companies to find "nicotine analogues" to replace nicotine in cigarettes provides an especially clear illustration that the industry regarded nicotine's primary effects as pharmacological, not flavor-related. The goal of this research was to develop a molecule that would "mimic nicotine's effect in the

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[721] *Id.* at 47 (emphasis added).

[722] *Regulation of Tobacco Products (Part 2): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 33 (Apr. 28, 1994) (testimony of Victor DeNoble). *See* AR (Vol. 708 Ref. 2).

[723] Pritchard WS (R.J. Reynolds Tobacco Co.), Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490. *See* AR (Vol. 3 Ref. 23-2).

[724] BATCO, *Method for Nicotine and Cotinine in Blood and Urine* (May 21, 1980), at 2. *See* AR (Vol. 23 Ref. 300-1).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

brain"[725] and "possess[] the desired features of brain stimulation and stress-relief"[726] not to find substitute compounds with the same flavor characteristics as nicotine.

Third, the manufacturers' contention that they blend for taste and not for pharmacological effects conflicts with their assertions that they blend and design their products to meet consumer preferences. As discussed above in sections II.A. and II.B., the primary reason consumers smoke is to satisfy their addiction and obtain the other pharmacological effects of nicotine, such as sedation and stimulation. This fact is widely accepted by both the scientific community and researchers and officials within the tobacco industry. Cigarette manufacturers that strive to satisfy smokers' demands must necessarily design and blend cigarettes that produce pharmacological effects, including satisfying the needs of addicted smokers. This issue is further discussed in section II.C.4.f., below.

The Agency does not find that flavor is irrelevant in the blending process. To the contrary, the Agency agrees that one of the objectives in tobacco blending is to provide flavorful cigarette smoke. In the competitive cigarette marketplace, a cigarette that satisfied consumers' pharmacological demands for nicotine but did not taste good would be unlikely to be a commercial success. RJR's experience with Premier may, in fact, confirm this point.

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[725] *Regulation of Tobacco Products (Part 2): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 33 (Apr. 28, 1994) (testimony of Victor DeNoble). *See* AR (Vol. 708 Ref. 2).

[726] Minutes of BATCO Research Conference at Hilton Head, SC (Sep. 24-30, 1968), at 3. *See* AR (Vol. 14 Ref. 172-2).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

The Agency finds, however, that a cigarette that tasted good but did not satisfy consumers' pharmacological demands for nicotine would be even more unlikely to be a commercial success. As Ian Uydess, the former Philip Morris scientist, states:

> [A] cigarette having satisfactory ('high enough') nicotine levels but marginal flavor, stood a better chance of being 'accepted' in the market place than a somewhat better tasting product with zero or ultra-low levels of nicotine ('not enough').
>
> . . . *Tobacco companies like Philip Morris learned a long time ago that it was hard to get people to stay with a good tasting product if the nicotine level was too low.*[727]

In other words, to produce a cigarette that smokers will find acceptable, the cigarette manufacturer must use tobacco blends that provide consumers the desired pharmacological effects of nicotine.

For these reasons, FDA concludes that cigarette manufacturers use nicotine-rich blends in low-tar cigarettes to ensure that these cigarettes deliver pharmacologically active doses of nicotine.

b. The Manufacturers Use Filtration and Ventilation Technologies That Selectively Remove More Tar than Nicotine and That Allow Smokers To Inhale More Nicotine than the Measured Levels

The evidence before the Agency also supports a finding that cigarette manufacturers use cigarette filters and ventilation to manipulate nicotine deliveries. Especially in low-tar products, the available evidence indicates that cigarette manufacturers and their filter suppliers have engineered filtration and ventilation systems to bring about greater reductions in tar than in nicotine, thereby increasing the nicotine/tar ratio. According to William Farone of Philip Morris, "modification of the construction of

[727] Declaration of Uydess II. (Feb. 29, 1996), at 11, 13 (emphasis added). *See* AR (Vol. 638 Ref. 1).

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the cigarette such as filter type, the type of filter material used, the number and placement of ventilation holes, [and] the density, composition and porosity of the cigarette paper" is the second principal means of controlling nicotine used by the industry.[728]

The effect of filtration and ventilation on nicotine deliveries is recognized in the technical tobacco literature. According to an article by a researcher at Lorillard Tobacco Co.:

> [V]entilated filters caused a significant drop in the amount of nicotine retained on the filter.
> *. . . [S]moke from ventilated cigarettes is relatively enriched in nicotine.*[729]

Similarly, scientists at Eastman Kodak Co., a manufacturer of cigarette filters, have observed that "*[a]s ventilation is increased, the nicotine content . . . increases markedly.*"[730]

Indeed, some filter manufacturers have openly promoted the ability of their filters to increase nicotine/tar ratios. For instance, Filtrona Ltd.'s Filtrona Ratio filter was promoted as "a new option available to cigarette designers which allows management of the yield ratios of important smoke components relative to tar, [including] . . . nicotine."[731]

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[728] Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 5. *See* AR (Vol. 638 Ref. 2).

[729] Norman V, Ihrig AM, Shoffner RA (Lorillard Tobacco Co.), The effect of tip dilution on the filtration efficiency of upstream and downstream segments of cigarette filters, *Beitrage zur Tabakforschung International*, Jul. 1984;12(4):178-185, at 184 (emphasis added). *See* AR (Vol. 103 Ref. 923).

[730] Kiefer JE (Eastman Kodak Co.), Ventilated filters and their effect on smoke composition, *Recent Advances in Tobacco Science* (1979), at 78. *See* AR (Vol. 28 Ref. 465).

[731] Papers, filters, and tipping, *Tobacco Reporter*, Apr. 1985;112(4):32. *See* AR (Vol. 351 Ref. 5624).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

When applied to commercial brands, this filter increased nicotine deliveries by over 25%, while leaving tar deliveries virtually unchanged.[732]

In their comments on the Jurisdictional Analysis, the cigarette manufacturers acknowledge that filtration and ventilation in low-tar cigarettes produce enhanced nicotine/tar ratios, but they argue that this is strictly an unavoidable physical phenomenon—not a design feature. The administrative record does not support their position.

Contrary to the cigarette manufacturers' contention, the filter manufacturers describe the role of filters and ventilation as not simply removing tar and nicotine according to immutable proportions determined by the laws of physics. Filters are highly engineered products that are "*designed exclusively to yield the maximum satisfaction from a carefully chosen tobacco blend.*"[733] The object of filters and ventilation is to "control the yield of the many constituents that the smoker receives" and to "*act[] more as a smoke modifier* than as an absolute filter which removes all particles of a known size."[734]

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As described above in section II.C.3.e., the administrative record indicates that filter manufacturers have developed numerous strategies for independently changing tar and nicotine deliveries. When the cigarette manufacturer selects a filter and ventilation design, therefore, the cigarette manufacturer's choices necessarily affect the relative

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[732] *Id.*

[733] Philips JA (Filtrona International Ltd.). Filters for cigarettes: an integral part of the cigarette, *Tobacco Reporter* (Oct. 1981), at 34 (emphasis added). *See* AR (Vol. 351 Ref. 5624).

[734] *Id.* at 34 (emphasis added).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

nicotine and tar deliveries. A decision to place the ventilation holes close to the tobacco rod will increase relative nicotine deliveries,[735] as will a decision to increase the porosity of the cigarette paper.[736] The use of increasingly porous perforated cigarette paper will "*selectively increase nicotine.*"[737] A decision to rely on relatively more ventilation and relatively less filtration is another "tool[]" that "increas[es] nicotine delivery without changing tar delivery."[738] Likewise, when manufacturers decide to increase the pH of the filter through use of an additive, this increases cigarette nicotine delivery "independently" of tar delivery.[739] Thus, contrary to the position of the cigarette manufacturers, there are many technical choices that manufacturers make in filtration and ventilation design that determine the extent to which the cigarette filter and ventilation will increase nicotine deliveries relative to tar deliveries.

The statement of William Farone corroborates the evidence showing that deliberate design decisions have caused the selective filtration and ventilation observed in

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[735] Kiefer JE (Eastman Kodak Co.), *Ventilated filters and their effect on smoke composition*, *Recent Advances in Tobacco Science* (1979), at 79. *See* AR (Vol. 28 Ref. 465).

[736] McMurtrie A, Lininger EF, Wu DT (Brown & Williamson), *Cigarette Paper Effects on Tar/Nicotine and CO/Tar Ratios*, 35th Tobacco Chemists' Research Conference, Winston-Salem, North Carolina (Oct. 6-9, 1981). *See* AR (Vol. 639 Ref. 2).

[737] Owens WF Jr. (Ecusta Paper and Film Group), *Effect of Cigarette Paper on Smoke Yield Composition*, 32d Tobacco Chemists' Research Conference, Montreal, Canada (1978) (emphasis added). *See* AR (Vol. 639 Ref. 10).

[738] Selke WA, *Making the cigarette do just what you want it to do*, *Journal Tobacco International* 1983:12. *See* AR (Vol. 102 Ref. 896).

[739] Lee BM (Eastman Kodak Co.), *Modification of Nicotine to Tar Ratio in Cigarette Smoke*, 42d Tobacco Chemists' Research Conference, Lexington, Kentucky (Oct. 2-5, 1988), at 33. *See* AR (Vol. 639 Ref. 2).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

low-tar cigarettes. According to Farone, "[t]he cigarette industry . . . *altered the cigarette filter in order to increase nicotine delivery.*"[740] Specifically, he states:

> *Filter design and ventilation allowed the design and manufacture of cigarettes that removed a higher percentage of tar than nicotine.* Selective filtration was accomplished by altering the technical specifications for a filter, e.g. by selecting different filter tow combinations, varying the denier per filament, and deciding whether or not to use additives in the filter. . . . *[A]ppropriate filters were identified to attain a predetermined nicotine/tar ratio.*[741]

The example of the regular-length Benson & Hedges filtered cigarettes that Congressman Henry A. Waxman described on the floor of the U.S. House of Representatives in July 1995 also contradicts the position of the cigarette industry.[742] The cigarette industry maintains that high nicotine/tar ratios are unavoidable in ultra-low-tar cigarettes because the high levels of filtration and ventilation in these cigarettes inevitably remove more tar than nicotine. The Benson & Hedges example, however, shows that (1) ultra-low-tar and nicotine levels can be achieved without increasing the ratio of nicotine to tar and (2) the high nicotine/tar ratios typically observed in cigarettes with ultra-low tar levels are therefore the result of deliberate design choices of manufacturers.

The Benson & Hedges cigarette was marketed as an ultra-low-tar cigarette from 1978 to 1985, with tar levels consistently below or near 1 milligram.[743] In three of those

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[740] Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 11 (emphasis added). *See* AR (Vol. 638 Ref. 2).

[741] *Id.* (emphasis added).

[742] Remarks of Waxman HA, 141 Cong. Rec. H8009-8010 (daily ed. Jul. 31, 1995). See AR (Vol. 27 Ref. 376a).

[743] *Id.*

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

years (1978, 1984, and 1985), the nicotine levels were also proportionately low, producing a normal nicotine/tar ratio.[744] Thus, in these years, the filtration and ventilation technologies used by the manufacturer to reduce tar deliveries did not selectively increase nicotine deliveries. In contrast, from 1979 to 1983, the nicotine levels were elevated relative to the tar levels, producing a high nicotine/tar ratio.[745] These changes in the nicotine/tar ratio were not due to chance.[746] These facts thus establish that the manufacturer, in this case Philip Morris, had the technical ability to achieve ultra-low-tar levels without causing nicotine levels to be relatively enhanced.

The evidence also indicates that cigarette manufacturers also use "elasticity" technologies, principally ventilation techniques that can be readily blocked, to allow smokers to increase their nicotine intakes above the levels measured on smoking machines. One example is Brown & Williamson's Barclay cigarette. This cigarette was first introduced as an ultra-low-tar cigarette in 1981. As noted above in section II.C.4.a.ii., tests in 1982 showed that the tobacco in the Barclay blend had a higher nicotine concentration than any other cigarette brand tested. Barclay also had more total nicotine in the tobacco rod than any other cigarette tested. For instance, Barclay had *over 60% more total nicotine* in the cigarette rod (12.80 mg per cigarette) than regular-strength Lucky Strike (7.92 mg per cigarette). Yet despite its high nicotine levels, Barclay had the second lowest nicotine yields of any cigarette tested, as measured by the FTC smoking machine method. Thus, even though, as noted, Barclay had over 60% more nicotine in

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[744] *Id.*

[745] *Id.*

[746] *Id.*

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the cigarette rod than the regular-strength Lucky Strike. its nicotine yield on the FTC smoking machine (0.15 mg per cigarette) was *90% lower* than the yield of the Lucky Strike (1.46 mg per cigarette).

Barclay was able to combine the highest total nicotine content with the second-lowest measured nicotine yield by relying on a "channel-ventilated" filter system. An investigation commenced by FTC in 1981 found that air flow through these channels is compromised during actual smoking and that, as a result, Barclay actually delivered considerably more nicotine and tar to the smoker than is obtained using the FTC's testing method. In 1983, the FTC successfully sued to enjoin Brown & Williamson from using nicotine, tar, and carbon monoxide results obtained from the FTC's smoking machines in Barclay advertising. *See* 60 FR 41718.

While Barclay is a striking example of a filter that delivers more nicotine to its smokers than to a smoking machine, the use of ventilation systems that can be blocked by smokers is common. As FDA reported in the Jurisdictional Analysis, the evidence in the record indicates that 32% to 69% of smokers of low-tar cigarettes block ventilation holes. *See* 60 FR 41717.

In sum, the evidence in the record supports a finding that the increase in nicotine deliveries relative to tar deliveries produced by selective filtration and ventilation result from the deliberate design choices of the manufacturers. The manufacturers do not persuasively refute this finding. Accordingly, the Agency finds that the manufacturers use filtration and ventilation technologies that are designed to selectively remove more tar than nicotine.

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c. The Manufacturers Use Chemical Additives to Increase the Delivery of "Free" Nicotine

The evidence in the record also supports a finding that the cigarette manufacturers control and manipulate nicotine deliveries through chemical manipulation. One way they do this is through the use of ammonia technologies that increase the delivery of "free" nicotine to smokers by raising the alkalinity or pH of tobacco smoke. "Free" nicotine is also sometimes referred to as "volatile," "extractable," or "non-ionized" nicotine. The use of ammonia compounds to increase pH is an outgrowth of the industry's product development research to improve the efficient use of smoke nicotine through pH modification. *See* section II.C.3., above.

The use of ammonia compounds is common in the cigarette industry. Ammonia compounds have been regularly identified in the list of cigarette ingredients submitted by the industry to the Department of Health and Human Services.[747] Indeed, the comments of the cigarette manufacturers concede that several ammonia-related compounds are used in the manufacture of cigarettes.[748]

An article in the *Wall Street Journal* describes the extent of the industry's reliance on ammonia technology.[749] According to the article, which is based on two major Brown & Williamson internal reports, Brown & Williamson adds ammonia compounds to "almost all" of its nonmenthol brands; Brown & Williamson views ammonia technology as "the

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[747] Joint Comment of Cigarette Manufacturers, Comment (Jan. 2, 1996), Vol. IV, at 84. *See* AR (Vol. 535 Ref. 96).

[748] *Id.*

[749] Freedman AM, Impact booster tobacco firm shows how ammonia spurs delivery of nicotine, *Wall Street Journal* (Oct. 18, 1995). *See* AR (Vol. 639 Ref. 2).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

soul of Marlboro" and "the key factor" that "makes Marlboro a Marlboro"; and Brown & Williamson found that ammonia technology was also used by RJR, Lorillard, and American Tobacco Co.[750] In congressional testimony, Thomas Sandefur, the CEO of Brown & Williamson, confirmed the widespread use of ammonia within the cigarette industry.[751]

It is well established that the addition of ammonia compounds to tobacco increases pH. This increase transforms nicotine that is "bound" in nicotine salts to "free" nicotine.[752] This effect is described in Brown & Williamson's 1991 "Handbook for Leaf Blenders and Product Developers," which states that "*[a]mmonia, when added to a tobacco blend, reacts with the indigenous nicotine salts and liberates free nicotine.*"[753]

Changing the chemical form of nicotine from a bound nicotine salt to free nicotine has several significant consequences, according to the evidence in the administrative record. First, it increases the quantity of nicotine that is transferred from the cigarette to

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[750] *Id.*

[751] *Regulation of Tobacco Products (Part 3): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 224-225 (Jun. 23, 1994) (statement of Thomas Sandefur). *See* AR (Vol. 709 Ref. 3).

[752] *See, e.g.*, Armitage AK, Turner DM, Absorption of nicotine in cigarette and cigar smoke through the oral mucosa, *Nature*, Jun. 27, 1970;226:1231-1232. *See* AR (Vol. 45 Ref. 25).

Surgeon General's Report, 1988, at 29. *See* AR (Vol. 129 Ref. 1592).

[753] *Regulation of Tobacco Products (Part 3): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 21 (Jun. 23, 1994) (statement of David Kessler) (emphasis added). *See* AR (Vol. 709 Ref. 3).

Brown & Williamson has acknowledged in its comment that the Handbook is a Brown & Williamson document. Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 37. *See* AR (Vol. 529 Ref. 104).

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the smoke. According to William Farone, the former director of applied research at Philip Morris:

> *The use of ammonia chemistry was important to the industry in maintaining adequate nicotine delivery to satisfy smokers. The industry was able to deliver more of the available nicotine in the blend to the smoker by using ammonia compounds. . . .* In the complex world of tobacco smoke chemistry, by increasing the pH of the aerosol in the mainstream smoke, more of the aerosol would be in the vapor phase and less in the liquid (or condensed) phase. *By increasing the ratio of vapor phase to liquid phase, one increases the total nicotine delivery since the condensed phase is less likely to survive the filter and the trip to the lungs.*[754]

Similarly, documents from the American Tobacco Company state:

> There has been an interest in increasing the amount of nicotine that is transferred from the tobacco to the mainstream smoke while leaving the "tar" level unchanged. Since most of the nicotine in tobacco is a non-volatile salt, *it was thought that a greater transfer would take place if the tobacco was made basic causing the nicotine to volatilize when the cigarette is smoked.*[755]

The second effect of increasing the free nicotine is to increase the amount of nicotine absorption that takes place in the mouth. It is well-established that free nicotine is significantly more absorbable than bound nicotine.[756] As early as 1968, researchers at BATCO, Brown & Williamson's parent, reported that there is a direct correlation between smoke pH and nicotine absorption in the mouth, stating that "[n]icotine retention appears

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[754] Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 13 (emphasis added). *See* AR (Vol. 638 Ref. 2).

[755] Bodenhamer NL (American Tobacco), Leaf Services Monthly Report for June (Jun. 30, 1980) (emphasis added). *See* AR (Vol. 27 Ref. 385).

[756] *See, e.g.*, Armitage AK, Turner DM. Absorption of nicotine in cigarette and cigar smoke through the oral mucosa. *Nature*, Jun. 27, 1970;226:1231-1232. *See* AR (Vol. 45 Ref. 25).

Surgeon General's Report, 1988, at 29. *See* AR (Vol. 129 Ref. 1592).

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to be dependent principally on smoke pH and nicotine content."[757] Similarly, RJR researchers have reported that:

> [B]y raising pH . . . from 6.0 to 6.5 [in a low-tar cigarette] you raise the level of nicotine that is transferred to the taste buds and body fluids in the mouth to the same level as with the higher tar cigarette. *And hence, even though the tar level has been dropped from 25 mg to 10 mg, by raising the pH from 6.0 to 6.5, you increase the nicotine transfer in the mouth. . . .*[758]

This effect of increased nicotine absorption in the mouth appears to be related to what some cigarette manufacturers describe as smoke "impact." For example, Brown & Williamson's Handbook for Leaf Blenders states that by adding ammonia:

> the ratio of extractable nicotine to bound nicotine in the smoke may be altered in favor of extractable nicotine. As we know, extractable nicotine contributes to impact in cigarette smoke and this is how ammonia can act as an impact booster.[759]

RJR describes this effect as "mouth satisfaction," which it distinguishes from "the ultimate satisfaction" which "comes from the nicotine which is extracted . . . in the lungs."[760]

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The third effect of increasing free nicotine appears to be to increase the rate of transfer of nicotine to the brain. This effect is discussed in a BATCO research paper

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[757] BATCO, *The Retention of Nicotine and Phenols in the Human Mouth* (1968), at BW-W2-11691. *See* AR (Vol. 445 Ref. 7593).

[758] Senkus M (R.J. Reynolds Tobacco Co.), *Some Effects of Smoking* (1976/1977), at 7 (emphasis added). *See* AR (Vol. 700 Ref. 593).

[759] *Regulation of Tobacco Products (Part 3): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 21 (Jun. 21, 1994) (statement of David Kessler). *See* AR (Vol. 709 Ref. 3).

[760] Senkus M (R.J. Reynolds Tobacco Co.), *Some Effects of Smoking* (1976/1977), at 7, 9. *See* AR (Vol. 700 Ref. 593).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

entitled "Further Work on Extractable Nicotine."[761] According to this report, when smoke is inhaled into the lungs, there is virtually complete retention of the nicotine, regardless of whether the nicotine is in its free or bound form. However, the report hypothesizes that the speed of absorption is different when free or extractable nicotine is increased and that "*with a higher 'extractable' nicotine, nicotine reaches the brain more quickly.*"[762] RJR researchers have also recognized that pH adjustments affect the speed of nicotine absorption, recommending that in designing cigarettes for new smokers "[t]he *rate* of absorption of nicotine should be kept low *by holding pH down*, probably below 6."[763]

FDA notes that the use of chemical manipulation to boost free nicotine levels may raise the amount of nicotine delivered to the smoker without a corresponding increase in nicotine yield, as measured by the FTC smoking machine. Thus, the actual nicotine delivery to the smoker from some brands may be higher than the FTC yield because of the addition of ammonia or similar compounds to increase free nicotine.

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Based on this evidence, the Agency finds that cigarette manufacturers manipulate and control nicotine deliveries through the use of ammonia compounds. These compounds transform bound nicotine to free nicotine. According to the industry's own documents, this transformation facilitates consumer use of cigarettes for pharmacological

[761] BATCO, *Further Work on 'Extractable' Nicotine* (1966), at BW-W2-11615 (emphasis added). *See* AR (Vol. 62 Ref. 308).

[762] *Id.* at 7 (emphasis added).

[763] Teague CE (R.J. Reynolds Tobacco Co.), *Research Planning Memorandum on Some Thoughts About New Brands of Cigarettes for the Youth Market* (Feb. 2, 1973), at 4 (emphasis added). *See* AR (Vol. 531 Ref. 125).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

purposes by: (1) increasing the amount of nicotine that is transferred from the tobacco to the smoke; (2) increasing the absorption of nicotine in the mouth; and (3) possibly increasing the speed of nicotine transfer to the brain.

d. Nicotine Deliveries Have Increased in Recent Years by Design, Especially in Low-Tar Cigarettes

The use of the methods described above, especially the use of nicotine-rich tobacco blends and selective filtration and ventilation, have increased nicotine deliveries to consumers. In the Jurisdictional Analysis, FDA found that nicotine deliveries as measured by the FTC smoking machine have been increasing since 1982, with the greatest increases occurring in the ultra-low-tar category. *See* 60 FR 41727–41730. These increases have been occurring without parallel increases in tar deliveries, thus indicating an industry-wide trend of designing cigarettes with enhanced nicotine deliveries.

The nicotine/tar ratios in low-tar cigarettes reflect these changes. The Agency's statistical analysis shows that, according to 1994 Federal Trade Commission data, the lowest-tar products had a markedly higher ratio of nicotine to tar than that found in higher-tar products. None of the 153 products with 14 or more milligrams of tar (the high-tar segment of the market) had a nicotine/tar ratio greater than 1 to 12. By contrast, 88 of the 93 products with 6 or fewer milligrams of tar (the ultra-low-tar segment) had a nicotine/tar ratio greater than 1 to 12. *See* 60 FR 41724. The industry did not challenge these figures in their comments.

The increase in nicotine/tar ratios has occurred primarily in the last two decades. In comparison with the 1994 results, only 2 of the 142 marketed cigarettes included in the FTC's report for 1972 had a nicotine/tar ratio greater than 1 to 12. Thus, the evidence

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from the reported nicotine and tar deliveries supports the conclusion that as the market for lower tar cigarettes grew over the last 25 years, manufacturers deliberately altered what had been the traditional ratio of nicotine to tar, increasing nicotine levels in relation to tar levels.[764]

This increase in the nicotine/tar ratios is persuasive evidence that the manufacturers design cigarettes to increase their relative nicotine deliveries. Without manufacturer intervention, nicotine levels tend to follow tar levels, because methods that reduce tar deliveries tend to reduce nicotine deliveries as well. As one industry executive testified before Congress, "[n]icotine levels follow the tar level. . . The correlation . . . is essentially perfect correlation between tar and nicotine."[765] The increase in nicotine deliveries relative to tar deliveries indicates that the manufacturers have taken affirmative steps to enhance nicotine deliveries.

The manufacturers dispute this finding. Although they first asserted that nicotine deliveries fall proportionately with tar deliveries, they now assert that the increase in nicotine/tar ratios is due to the unavoidable effects of filtration and ventilation—not any intentional actions of the manufacturers. The record does not support the industry's assertion, however. First, as discussed in section II.C.4.a.ii., above, the cigarette

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[764] Federal Trade Commission. *Report of the "Tar" and Nicotine Content of 142 Varieties of Cigarettes* (Jul. 1972). *See* AR (Vol. 314 Ref. 4856). On a percentage basis, only 1.4% of the 1972 products had a nicotine/tar ratio greater than 1 to 12. In 1994, that figure grew to 26.3% overall, and rose to 95% for the 93 products in the lowest tar category. *Id.*; Federal Trade Commission, *Tar, Nicotine, and Carbon Monoxide of the Smoke of 933 Varieties of Domestic Cigarettes* (1994). *See* AR (Vol. 29 Ref. 485).

[765] *Regulation of Tobacco Products (Part 1): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 143, 378 (Mar. 25, 1994) (statement of Alexander Spears). *See* AR (Vol. 707 Ref. 1).

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manufacturers deliberately use tobacco blends with the highest nicotine concentrations in the lowest tar cigarettes.

Second, the record contradicts the industry's contention that they do not control the extent to which filtration and ventilation selectively reduce tar more than nicotine. Indeed, the record indicates that the manufacturers affirmatively use filtration and ventilation to enhance nicotine/tar ratios. *See* section II.C.4.b., above.

Moreover, as the Agency reported in the Jurisdictional Analysis, increases in nicotine deliveries relative to tar deliveries have occurred in all categories of cigarettes. Although the increases in nicotine delivery are largest among the ultra-low-tar cigarettes, relative nicotine deliveries have also been increasing in low-tar and high-tar cigarettes. *See* 60 FR 41727–41731. The manufacturers' theory regarding the unavoidable effects of filtration and ventilation in ultra-low-tar cigarettes cannot explain these other increases in relative nicotine deliveries.

The evidence in the record provides specific examples where manufacturers appear to have designed cigarettes to achieve enhanced nicotine deliveries. As discussed in section II.C.3.b., above, for example, RJR researchers in the mid-1970's recommended "*maintaining the nicotine as high as possible*" in low-tar cigarettes.[766] Researchers specifically recommended that RJR develop a new brand that would deliver 5 mg tar and 0.5 to 0.8 mg nicotine, stating that "*on inhalation into the lungs, 0.5 to 0.8 mg of nicotine*

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[766] Senkus M (R.J. Reynolds Tobacco Co.), *Some Effects of Smoking* (1976/1977), at 10 (emphasis added). *See* AR (Vol. 700 Ref. 593).

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would provide sufficient nicotine to the blood to produce the stimulation and relaxation effects desired by the smoker."[767]

In the late 1970's and 1980's, RJR began to market ultra-low-tar cigarettes that met these specifications. For instance, RJR first introduced an ultra-light version of its Winston brand in 1981. That year, the Winston Ultra Lights 100's had a tar delivery of 5 mg and a nicotine delivery of 0.5 mg—exactly the deliveries recommended by its researchers as providing the sufficient nicotine to provide the pharmacological effects sought by consumers.[768] As recently as 1994, both the king-size Winston Ultra Lights (hard pack) and the Winston Ultra Lights 100's (hard pack) continued to have these recommended deliveries of 5 mg tar and 0.5 mg. nicotine, as did king-size Camel Ultra Lights and several other RJR ultra-low-tar brands.[769]

Another example of deliberate design to achieve relatively enhanced nicotine deliveries appears to be the Merit Ultra Lights by Philip Morris. Philip Morris researchers conducted extensive research in the 1970's to determine "what combinations of tar and nicotine make for optimal acceptibility in a low delivery cigarette."[770] This research concluded that a higher nicotine/tar ratio (at least 0.09), compared to the natural ratio of

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[767] *Id.* at 11-12 (emphasis added).

[768] Federal Trade Commission, *"Tar," Nicotine and Carbon Monoxide of the Smoke of 200 Varieties of Cigarettes* (1981). *See* AR (Vol. 535 Ref. 96, vol. III.D).

[769] Federal Trade Commission, *Tar, Nicotine, and Carbon Monoxide of the Smoke of 933 Varieties of Domestic Cigarettes* (1994). *See* AR (Vol. 29 Ref. 485).

[770] Dunn WL, Johnston M, Ryan F (Philip Morris Inc.), *Plans for 1972* (Sep. 8, 1971), in 141 Cong. Rec. H8128 (daily ed. Aug. 1, 1995). *See* AR (Vol. 711 Ref. 6).

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0.07, was optimal.[771] Similarly, shortly thereafter, Philip Morris introduced the king-size Merit Ultra Lights with an elevated nicotine/tar ratio of approximately 0.10.[772] The king-size Merit Ultra Lights (hard pack) continued to have an elevated nicotine/tar ratio of 0.10 as recently in 1994.[773] According to William Farone, the former director of applied research at Philip Morris, the Merit Ultra Lights is an example of "a blend change incorporating the greater use of higher nicotine tobacco . . . [to] produce *a low tar cigarette with the desired pharmacologically active level of nicotine.*"[774]

These brands do not appear to be isolated examples. The evidence in the record indicates that the design of cigarettes to achieve specific nicotine deliveries is a common practice within the cigarette industry. According to Farone, cigarettes are designed to "attain a *predetermined nicotine/tar ratio.*"[775] Likewise, Ian Uydess, the former Philip Morris scientist, states that "*[n]icotine levels were routinely targeted and adjusted by Philip Morris.*"[776]

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[771] Jones B, Houck W, Martin P (Philip Morris Inc.), *Low Delivery Cigarettes and Increased Nicotine/Tar Ratios, A Replication* (Oct. 1975), in 141 Cong. Rec. H8132 (daily ed. Aug. 1, 1995) (emphasis added). *See* AR (Vol. 711 Ref. 6).

[772] Federal Trade Commission, *"Tar," Nicotine, and Carbon Monoxide of the Smoke of 200 Varieties of Cigarettes* (1981). *See* AR (Vol. 535 Ref. 96, vol. IILD).

[773] Federal Trade Commission, *Tar, Nicotine, and Carbon Monoxide of the Smoke of 933 Varieties of Domestic Cigarettes* (1994). *See* AR (Vol. 29 Ref. 485).

[774] Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 10 (emphasis added). *See* AR (Vol. 638 Ref. 2).

[775] *Id.* at 11 (emphasis added).

[776] Declaration of Uydess IL (Feb. 29, 1996), at 8 (emphasis added). *See* AR (Vol. 638 Ref. 1).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

e. The Manufacturers Precisely Control Nicotine Deliveries

A principal feature of all marketed cigarettes is the precise control over nicotine delivery achieved by the manufacturers. Annual variations in the nicotine content of raw tobacco leaves originating in the same geographical area can be as high as 100%.[777] Nevertheless, the nicotine deliveries in commercial cigarettes are consistent to a tenth of 1%. *See* 60 FR 41694. This is a high degree of control even for a conventional pharmaceutical company. It does not occur by chance, and the industry does not pretend that it does. The precise control ensures that smokers receive a consistent nicotine dosage within a brand from cigarette to cigarette, pack to pack, and year to year.

The evidence in the record supports a finding that the manufacturers' precise control over nicotine levels reflects the central role of nicotine in cigarette manufacturing. According to the statement of William Farone of Philip Morris, the cigarette industry even developed "complex computer models to help determine nicotine and tar deliveries."[778] These models "allowed blend ingredients, filter and paper components, and numerous other variables to be considered simultaneously" and "enabled product developers to identify which components were required to produce specific nicotine and tar deliveries."[779]

The administrative record demonstrates that the industry pays careful attention to nicotine throughout the manufacturing process. In particular, as described below, nicotine

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[777] Joint Comment of Cigarette Manufacturers, Comment (Jan. 2, 1996), Vol. IV, at 32. *See* AR (Vol. 535 Ref. 96).

[778] Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 13. *See* AR (Vol. 638 Ref. 2).

[779] *Id.* at 13-14.

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plays an essential role in tobacco growing, leaf purchasing, leaf blending, and the manufacture of reconstituted tobacco. This control provides smokers seeking the pharmacological effects of nictine with a remarkably consistent dose of nicotine from cigarette to cigarette.

i. Tobacco Growing. Cigarette manufacturers' ability to control nicotine delivery begins with tobacco growing. Although cigarette manufacturers do not directly control what tobacco farmers grow, they have successfully influenced the characteristics of tobacco crops, including their nicotine content.

As discussed in the Jurisdictional Analysis, cigarette manufacturers were influential in establishing the Minimum Standards Program (MSP) administered by the USDA. This program began in the 1960's in response to the emergence of so-called "discount" varieties of tobacco that had low nicotine contents. The MSP eliminated the discount varieties and helped control the variation in the nicotine content of the tobacco crop by setting minimum and maximum permissible levels of nicotine. *See* 60 FR 41697–41698.

Moreover, tobacco leaf experts have reported that the nicotine level in certain varieties of tobacco rose in response to the needs of cigarette manufacturers. For instance, an expert with a U.S. leaf company observed in 1983 that "[o]nce the manufacturer has expressed a preference for a certain style of leaf, cultural practices can be implemented on the farm to try to fulfill his requirements."[780] According to this expert,

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[780] Glass JM, Production and leaf chemistry of burley tobacco in Latin America, in *Recent Advances in Tobacco Science*, 37th Tobacco Chemists' Research Conference (1983), at 81. *See* AR (Vol. 528 Ref. 97, appendix 19).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

"a noticeable change has occurred in leaf chemistry" of burley tobacco imported into the United States—"*especially the increase in nicotine levels.*"[781]

ii. Leaf Purchasing. The industry's direct control over nicotine delivery starts with its leaf purchasing decisions. As described in the Jurisdictional Analysis, *see* 60 FR 41703–41706, and as the industry comments themselves confirm, important leaf characteristics in purchasing include "stalk position," "impact," and "smoke quality." These characteristics correlate closely with the nicotine content in the tobacco leaves.

The industry acknowledges that, as a general rule, the relative position of a tobacco leaf on the stalk of the plant will determine the nicotine content in that leaf.[782] The nicotine level usually goes up from the bottom to the top of the stalk. According to Brown & Williamson's comment, "*[h]igher stalk tobacco leaves do have more nicotine than lower stalk leaves on the same plant.*"[783]

The Agency has found that stalk position plays a key role in the leaf purchasing practices of cigarette manufacturers. The industry does not dispute the significance of stalk position. For example, Brown & Williamson does not dispute the Agency's finding that stalk position is the "first thing" Brown & Williamson looks for during leaf purchasing. *See* 60 FR 41705. Similarly, RJR concedes that stalk position is one of the three primary "quality determinants" used by RJR in leaf purchasing.[784] Because of the

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[781] *Id.* at 77 (emphasis added).

[782] R.J. Reynolds Tobacco Co., Comment (Jan. 2, 1996), at 44. *See* AR (Vol. 519 Ref. 103).

Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 10. *See* AR (Vol. 529 Ref. 104).

[783] Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 10 (emphasis added). *See* AR (Vol. 529 Ref. 104).

[784] R.J. Reynolds Tobacco Co., Comment (Jan. 2, 1996), at 44. *See* AR (Vol. 519 Ref. 103).

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relationship between stalk position and nicotine content, when manufacturers select tobacco leaves based on stalk position, they are in effect controlling the nicotine content of the leaves they purchase.

It is also undisputed that "impact" is associated with the nicotine level in a tobacco leaf and that "impact" plays a role in leaf purchasing. RJR, for instance, admits that "impact is . . . an element of any smoking of tobacco, including smoking of samples purchased during the auction season;" and that "nicotine is reported to be a factor" in "impact."[785]

Cigarette manufacturers deny that nicotine plays a role in leaf selection. In their words, "nicotine content is not a principal criterion in the purchase of leaf."[786] The Agency does not find this assertion to be credible. Finished cigarettes have highly consistent nicotine deliveries. This control could not be achieved without taking into account nicotine content in the purchase of tobacco leaves. If nicotine content was not a critical purchasing factor, manufacturers would have no assurance that they were purchasing leaves that could be blended together to provide consistent nicotine deliveries in the finished cigarettes.

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iii. Leaf Blending. Leaf blending is one of the primary means the industry uses to control nicotine levels in cigarettes. This is acknowledged by the industry, which states in its joint comment that "[t]obacco is blended for consistency and uniformity. . . ."[787] At

[785] *Id.* at 43-44.

[786] Joint Comment of Cigarette Manufacturers, Comment (Jan. 2, 1996), Vol. IV, at 58. *See* AR (Vol. 535 Ref. 96).

[787] *Id.* at 66.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

a minimum, therefore, the industry has conceded one of the Agency's points in its Jurisdictional Analysis: blending to ensure "consistency and uniformity" enables the industry to overcome naturally occurring variations in nicotine associated with genetics and soil and climatic conditions. *See* 60 FR 41706.

The joint industry comment provides a graphic representation of the naturally occurring variations in nicotine levels in raw tobacco. The industry's submission shows the rising but substantially fluctuating nicotine levels in flue-cured tobacco from the early 1950's through the early 1990's.[788] Through blending, tobacco manufacturers are able to overcome these variations and produce a remarkably consistent product with uniform nicotine levels.

The central role of blending in ensuring consistent nicotine yields is acknowledged in the industry comments. As Brown & Williamson observes, "the manufacturing challenge is to maintain constancy of product composition not only from day to day, but month to month and year to year despite variation in the raw material."[789]

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iv. Reconstituted Tobacco. The tobacco industry also pays careful attention to nicotine during the manufacture of reconstituted tobacco, which makes up about 15% to 25% of the tobacco in cigarettes.[790] The process of manufacturing reconstituted tobacco is described in detail in the Jurisdictional Analysis. *See* 60 FR 41719–41721. The careful management of nicotine in this process allows the manufacturers to control precisely the level of nicotine in reconstituted tobacco.

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[788] *Id.* at Vol. IV, Fig. 1.

[789] Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 17. *See* AR (Vol. 529 Ref. 104).

[790] Joint Comment of Cigarette Manufacturers, Comment (Jan. 2, 1996), Vol. IV, at 72. *See* AR (Vol. 535 Ref. 96).

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II.C.4.

The statement of William Farone, the former Philip Morris director of applied research, describes how "the industry has used reconstituted tobacco products to assist in controlling the nicotine delivery in cigarettes."[791] According to Farone:

> By controlling the ingredients that go into making reconstituted tobacco, the industry controls the chemical and physical properties of the finished sheet, *including its nicotine content*. . . . The reconstituted tobacco blend destined for a low tar cigarette can be made with a higher concentration of [high-nicotine] burley tobacco scraps than the blend of reconstituted tobacco designated for a full flavor brand.[792]

Farone also describes how cigarette manufacturers monitor nicotine levels in reconstituted tobacco, stating that "[q]uality control checks involving the use of a gas or liquid chromatography to ascertain the exact nicotine amounts are routinely employed during the process."[793] In its comments, Philip Morris confirms that it regularly measures nicotine levels in reconstituted tobacco. According to Philip Morris' comments:

> Representative periodic sampling is done with respect to all tobacco materials that go into the cigarette manufacturing process—natural leaf tobacco, expanded tobacco, as well as blended and reconstituted leaf. *Such periodic sampling includes measurements of . . . alkaloids or nicotine.*[794]

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[791] Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 12. *See* AR (Vol. 638 Ref. 2).

[792] *Id.*

[793] *Id.*

[794] Philip Morris Inc., Comment (Apr. 19, 1996), at 56 (emphasis added). *See* AR (Vol. 700 Ref. 226).

The Agency also received a declaration relating to reconstituted tobacco from Jerome Rivers, a former supervisor in Philip Morris' Blended Leaf Plant, Declaration of Rivers J (Mar. 7, 1996). *See* AR (Vol. 640 Ref. 3), as well as two affidavits from current Philip Morris employees denying some of Rivers' assertions (Philip Morris Inc., Comment (Apr. 19, 1996), Appendix 3. *See* AR (Vol. 700 Ref. 226)), and supplemental comments relating to Rivers' declaration submitted by Philip Morris after the close of the comment period. Philip Morris Inc., Supplemental Comments (May 30, 1996). *See* AR (Vol. 700 Ref. 1331). After considering Rivers' declaration, the two affidavits, and Philip Morris' original and supplemental comments, the Agency has determined that it will not rely on the Rivers declaration or the two affidavits.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

There is also evidence that reconstituted tobacco is used by cigarette manufacturers as a vehicle for the addition of ammonia compounds. An article in the *Wall Street Journal* reports that Philip Morris, Brown & Williamson, and R.J. Reynolds add ammonia to their reconstituted tobacco.[795] According to the article, internal Brown & Williamson documents describe the "nicotine pick-up potential" of ammonia in reconstituted tobacco. The tobacco company documents described in the article state that ammonia added to reconstituted tobacco can scavenge nicotine from the tobacco in the rest of the cigarette, significantly increasing the level of "free nicotine" in the cigarette. One of the documents, a Brown & Williamson competitive analysis of Marlboro, states that ammonia-treated reconstituted tobacco is "the soul of Marlboro."[796]

As a result of the industry's focus on nicotine in the areas described above, as well as in other areas described in the Jurisdictional Analysis, cigarette manufacturers provide smokers seeking the pharmacological effects of nicotine with a remarkably consistent dose of nicotine from cigarette to cigarette.

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f. Satisfying Consumer Preferences Requires Controlling and Manipulating Nicotine Deliveries to Satisfy Addiction and Provide Other Pharmacological Effects

The cigarette industry maintains that it does not control and manipulate nicotine deliveries because its sole objective is to design cigarettes that meet consumer preferences. Brown & Williamson, for example, asserts that:

> [I]ts intent is to design, manufacture and market its cigarettes to meet the preferences of adult smokers over competing brands, not to create and maintain addiction. . . . Consumer demand determines

[795] Freedman AM, Tobacco firm shows how ammonia spurs delivery of nicotine, *Wall Street Journal* (Oct. 18, 1995). *See* AR (Vol. 639 Ref. 2).

[796] *Id.*

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

the content of the tobacco blends used in marketed B&W cigarettes.[797]

Similarly, RJR asserts that it "designs, manufactures, and markets a broad range of cigarette products in response to the . . . demands of adult smokers" and "not . . . to provide smokers with pharmacologically active 'doses' of nicotine."[798]

The Agency agrees that cigarette manufacturers, like other manufacturers of consumer products, design their products to meet consumer demand. The Agency disagrees, however, that this establishes that cigarette manufacturers do not control and manipulate nicotine levels for pharmacological purposes. The unstated premise of the manufacturers' argument is that the consumer demands they seek to satisfy do *not* include a desire for the pharmacological effects of nicotine. This is simply not credible. To the contrary, the Agency finds that what the cigarette manufacturers describe as satisfying consumer preferences is, in reality, providing consumers with cigarettes that sustain consumers' addiction and offer other desired pharmacological effects of nicotine.

It is beyond reasonable dispute that consumers of cigarettes smoke for the pharmacological effects of nicotine, including satisfaction of their addiction. As discussed in sections II.A. and II.B., above, this fact is widely accepted in the scientific community. As discussed in section II.C.2. and 3., above, this fact is also accepted by the cigarette manufacturers' own scientists. The implication of this fact for cigarette design is clear: to compete in the marketplace, cigarette manufacturers must produce cigarettes that sustain

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[797] Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 3, 12 (emphasis added). *See* AR (Vol. 529 Ref. 104).

[798] R.J. Reynolds Tobacco Co., Comment (Jan. 2, 1996), at 3-4. *See* AR (Vol. 519 Ref. 103).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

smokers' addiction and provide the other pharmacological effects of nicotine sought by smokers. Any cigarette manufacturer that failed to provide these pharmacological effects would soon find itself out of business, because addicted smokers and other smokers seeking the pharmacological effects of nicotine would switch to other brands.

Brown & Williamson provides an example of how meeting consumer preferences compels cigarette manufacturers to control and manipulate nicotine. As noted above, Brown & Williamson's comments assert that Brown & Williamson designs its cigarettes to meet "consumer demands." As discussed above in section II.C.2.c., however, the documents in the record from Brown & Williamson and its parent, BATCO, also acknowledge that "*a considerable proportion of smokers depend on the pharmacological action of nicotine for their motivation to continue smoking*"[799] and that "*nicotine plays a predominant role for many smokers.*"[800] Indeed, as recently as 1992, company researchers stated that what "*the smoker clearly wants*" is "*[t]he rapid, peaking intake of nicotine.*"[801] Both Brown & Williamson's assertion that it designs cigarettes to meet "consumer demands" and its acknowledgment that smokers seek "the pharmacological action of nicotine" leads to an obvious conclusion: Brown & Williamson's efforts to meet consumer preferences necessarily require the company to design cigarettes that provide consumers with the pharmacological effects of nicotine.

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[799] Kilburn KD, Underwood JG (BATCO), *Preparation and Properties of Nicotine Analogues* (Nov. 9, 1972), at 2 (emphasis added). *See* AR (Vol. 31 Ref. 524-1).

[800] Green SJ (BATCO), *BAT Group Research* (Sep. 4, 1968), at 2 (emphasis added). *See* AR (Vol. 15 Ref. 192).

[801] *Transdermal Nicotine*, Research and Development/Quality, at 3 (emphasis added). *See* AR (Vol. 531 Ref. 125).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

Documents in the administrative record confirm that in designing cigarettes to meet "consumer demands," the cigarette manufacturers carefully take into account consumers' pharmacological need for nicotine. One example is Project Wheat. As discussed above in section II.C.3.c.ii., BATCO conducted Project Wheat in the mid-1970's to determine smokers' "Inner Need" for nicotine.[202] BATCO undertook this

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The process of "consumer preference testing," which is described in the comments of the cigarette manufacturers, is one of the ways the manufacturers refine nicotine deliveries. In its comments, Brown & Williamson explains that it asks consumers to rate prototype cigarettes to determine if its tobacco blends produce "satisfaction," "strength," and other desirable attributes to consumers. According to Brown & Williamson, "satisfaction," as used in consumer preference testing, "reflects the consumer's total reaction to the total smoking experience delivered by the cigarettes."[806] If consumer testing shows that a Brown & Williamson cigarette produces insufficient satisfaction, Brown & Williamson says its product developers will "adjust product recipes and designs to improve or maintain product preference."[807]

In reality, however, Brown & Williamson knows that nicotine's pharmacological effects play the primary role in consumer "satisfaction." For instance, in 1983, BATCO researchers reported their "basic assumption" that "*nicotine. . . . is almost certainly the key smoke component for satisfaction.*"[808] Likewise, in a 1984 conference, the BATCO researchers reported that "'*satisfaction' must be related to nicotine.* Many people believe it [is] a 'whole body response' and *involves the action of nicotine in the brain.*"[809] Thus, Brown & Williamson understands that reports of inadequate satisfaction in consumer preference testing can signal a need to enhance nicotine deliveries.

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[806] Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 8. *See* AR (Vol. 529 Ref. 104).

[807] *Id.* at 9.

[808] Minutes of BATCO Research Conference at Rio de Janeiro (Aug. 22-26, 1983), at 10 (emphasis added). *See* AR (Vol. 22 Ref. 287-5).

[809] BATCO. *Conference Outline* (Jun. 6-8, 1984), at BW-W2-01977 (citation omitted) (emphasis added). *See* AR (Vol. 22 Ref. 287-6).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

The statements of William Farone, the former Philip Morris director of applied research, and Ian Uydess, the former Philip Morris scientist, make precisely this point. They confirm that product developers for the cigarette manufacturers do in fact adjust nicotine levels during consumer testing. According to Farone:

> *This concept of nicotine delivery being essential to consumer satisfaction was common knowledge within Philip Morris and the rest of the industry. When consumer testing indicated that a product was lacking in "impact" or some similar descriptor that could be associated with nicotine, experienced market researchers and product developers would compensate by increasing nicotine levels . . . .*[810]

Similarly, Ian Uydess states:

> In the case of nicotine, specific levels of nicotine would be targeted in the test products (test 'articles') in a range that extended from 'ultra-low' (or even zero) nicotine deliveries, to deliveries equal to, or slightly above that found in some of their own (or a competitor's) 'full-flavor' or 'full-bodied' products. This was done to examine how the smoker would react to various nicotine levels as a predictor of how well these products might do in the market with specific regard to: "not enough nicotine", "an acceptable level of nicotine", or "too much nicotine."[811]

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Thus, the Agency concludes that the manufacturers' explanation for their actions does not withstand scrutiny. Overwhelming evidence establishes that smokers seek the pharmacological effects of nicotine from cigarettes. *See* section II.A. and II.B., above. Overwhelming evidence also establishes that the manufacturers know that. *See* section II.C.2., above. Manufacturers that design their products to meet consumer demands that

[810] Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 8 (emphasis added). *See* AR (Vol. 638 Ref. 2).

[811] Declaration of Uydess IL (Feb. 29, 1996), at 11. *See* AR (Vol. 638 Ref. 1).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

they know are pharmacological in nature are necessarily engaged in designing products to provide pharmacological effects.

In sum, the evidence discussed in this section discloses that the manufacturers use several methods to control and manipulate nicotine deliveries in commercial cigarettes. These design features include: (1) the use of various tobacco blends with varying nicotine levels; (2) filter ventilation and related technologies that selectively remove more tar than nicotine and allow smokers to obtain more nicotine than the measured FTC yields; and (3) the use of ammonia technologies that increase the delivery of "free" nicotine. In addition, the evidence shows that the manufacturers control nicotine levels in virtually all aspects of cigarette manufacture, thereby ensuring that smokers receive a consistent nicotine delivery in each cigarette. Combined with the evidence regarding product research and development in section II.C.3., this evidence shows that the manufacturers "design" cigarettes to provide a consistent, pharmacologically active dose of nicotine to smokers, thereby establishing that cigarettes are "intended" to affect the structure and function of the body.

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5. Conclusion

The Agency's role in determining intended use through the statements, research, and actions of the manufacturer is to be a fact finder. In this case, after careful consideration of the evidence and the comments, the Agency finds that the evidence of cigarette manufacturers' statements, research, and actions demonstrates that cigarettes are intended to cause significant pharmacological effects in smokers. The Agency makes this finding for three principal reasons.

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II.C.5.

First, as described in section II.C.2., above, the evidence shows that the cigarette manufacturers are aware of and have exhaustively studied the pharmacological effects and uses of nicotine. In the case of Philip Morris, RJR, and Brown & Williamson, the manufacturers conducted extensive in-house research on the pharmacological effects and uses of nicotine. Their researchers and officials repeatedly expressed the view that nicotine causes pharmacological effects, that consumers smoke cigarettes to obtain these effects, and that cigarettes are delivery devices for nicotine. The evidence further shows that the cigarette manufacturers as a group funded extensive research into nicotine pharmacology through the Council for Tobacco Research. This evidence establishes that the manufacturers "have in mind" that cigarettes will be used for the particular purpose of delivering the pharmacological effects of nicotine to smokers.

Second, the evidence in sections II.C.3. and II.C.4. shows that the cigarette manufacturers "design" cigarettes to have pharmacological effects. This evidence reveals that the manufacturers have conducted extensive product research and development to identify pharmacologically active doses of nicotine and to optimize the delivery of nicotine to smokers and that company researchers repeatedly recommended the development of cigarettes that maintain adequate nicotine deliveries.

This evidence also shows that the cigarette manufacturers carefully control and manipulate the nicotine delivery of their commercially marketed cigarettes to provide smokers with a pharmacologically active dose of nicotine. Among other practices, the manufacturers use high-nicotine blends that increase nicotine deliveries in their lowest-tar products; rely on filtration and ventilation technologies that selectively remove more tar than nicotine; add ammonia compounds that increase the delivery of "free" nicotine; and

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carefully control the nicotine level in all cigarettes. Through the use of these practices, the cigarette manufacturers are able to deliver sufficient nicotine to satisfy consumers. An inevitable consequence of these practices is to keep consumers smoking by sustaining their addiction.

Third, the manufacturers have been unable to provide a convincing explanation that refutes either the evidence showing that they have in mind the pharmacological effects and uses of cigarettes or the evidence showing that they have designed cigarettes to provide these effects. This failure is significant because the manufacturers alone have access to the company documents and other information that would provide a complete explanation of their knowledge and design practices. The absence of a credible counter-explanation by the persons best situated to explain the evidence before the Agency adds additional support for the Agency's findings.

Under the legal standards described in section II.C.1., above, the evidence that the manufacturers (1) "have in mind" that cigarettes will be used for pharmacological purposes and (2) "design" cigarettes to deliver a pharmacologically active dose of nicotine each provides an independent basis for establishing intended use. Taken together, the two categories of evidence are consistent with each other and mutually reinforcing. Taken as a whole, therefore, the evidence from the statements, research, and actions of the manufacturers amply supports the finding that the effects of cigarettes on the structure and function of the body are "intended" by the cigarette manufacturers.

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6. Response to Comments

a. Comments on Statements and Research on Nicotine's Drug Effects

i. Comments on Specific Philip Morris Statements and Research Projects. In July 1995, a large number of Philip Morris internal documents reflecting over a decade of its research on smoking motivation were published in the *Congressional Record*. A smaller number of documents from Philip Morris became available as a result of a lawsuit brought against Philip Morris by a smoker.[812] In its Jurisdictional Analysis, FDA reproduced statements from those documents as evidence that company officials believed that consumers use cigarettes to obtain the pharmacological effects of nicotine.

A comment submitted by Philip Morris argues that the documents do not provide such evidence because FDA allegedly mischaracterized or took out of context some of the quotes from the documents. Philip Morris argues that: (1) other statements in the documents show that Philip Morris researchers were actually uncertain why people smoke; (2) in addition to studies on the pharmacological motivations for smoking, Philip Morris conducted studies on other motives for smoking, demonstrating that Philip Morris did not believe that pharmacological motives for smoking were primary; (3) FDA omitted passages from the documents that would have cast them in a different light; and (4) some of the statements cited by FDA were actually only hypotheses of Philip Morris researchers, or the hypotheses of outside researchers, which were not ultimately supported by the results of their studies.

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[812] *Cipollone v. Liggett Group Inc.*, No. 83-2864 (D.N.J. dismissed Nov. 3, 1992).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

FDA has reviewed all of the publicly available documents written by Philip Morris officials. The Agency has concluded that, both individually and as a whole, they demonstrate that Philip Morris conducted extensive, sophisticated research on the pharmacological effects of nicotine in cigarettes and the pharmacological motives for smoking, and that officials responsible for research and development at all levels of the company expressed consistent beliefs throughout the period covered by the documents that the pharmacological effects of nicotine were the primary reason people smoke. The documents also demonstrate that these beliefs, and the data supporting them, were held by and communicated to company executives, including the board of directors. Below, FDA addresses each of Philip Morris' arguments, with examples from individual documents claimed by Philip Morris to have been mischaracterized. In every case, the documents speak for themselves.

1. Philip Morris argues that it conducted studies on other motives for smoking, demonstrating that Philip Morris did not believe that pharmacological motives for smoking were primary. Philip Morris cites a single document from 1970 for this premise.

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FDA has reviewed the studies on smoking motivation referred to in the publicly available Philip Morris documents. The relative importance Philip Morris placed on pharmacological motives for smoking compared to other motives is clear from these studies. The vast majority of the company's studies were conducted to assess the pharmacological effects of, and motives for, smoking. A small minority of the studies were intended to assess other reasons for smoking. Indeed, the research documents show that Philip Morris' focus on the pharmacological effects of nicotine increased over time.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

By the early 1980's, when the large collection of documents made public by Congress end, Philip Morris' research on smoking motivation was overwhelmingly dominated by research on the pharmacological effects of nicotine. A 1980 report, for instance, describes fifteen major studies—eleven of which examined various aspects of nicotine's pharmacological effects on smokers and on dose-regulating behavior by smokers.[813] The nicotine-related studies included:

(1) Studies on the effects of cigarettes and nicotine on electrical and chemical activity in the human brain. The objectives of this program are described as follows:

> It is our belief that the reinforcing properties of cigarette smoking are directly relatable to the effects that smoking has on electrical and chemical events within the central nervous system. Therefore, the goals of the electrophysiology program are to: (I) Determine how cigarette smoking affects the electrical activity of the brain, and (II) Identify, as far as possible, the neural elements which mediate cigarette smoking's reinforcing actions.[814]

(2) Studies on rats demonstrating that nicotine is "reinforcing" (causes animals to "self-administ[er]" nicotine, i.e., seek repeated doses), tests positive in drug discrimination tests which can predict whether a substance has mood-altering effects in humans, and acts centrally in the brain. The objectives of this program include "(I) To develop a better understanding of the behavioral pharmacological actions of nicotine, particularly the action which reinforces smoking behavior."[815]

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[813] Dillin WL (Philip Morris Inc.), *Plans and Objectives–1981* (Nov. 26, 1980), in 141 Cong. Rec. H7681–7683 (daily ed. Jul. 25, 1995). See AR (Vol. 14 Ref. 175a).

[814] *Id.* at H7681.

[815] *Id.* at H7682.

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(3) Studies on the level of nicotine in saliva over time, and on the correlation of salivary nicotine levels to blood nicotine levels, to answer the question, "Does a low systemic level of nicotine trigger the smoking response?"[816]

Philip Morris provides no additional or later documents that would suggest that these studies are not representative. Thus, the extensive and sustained investigation into nicotine pharmacology reflected in Philip Morris' documents demonstrates that its researchers believed that the pharmacological effects of nicotine were the primary reason for smoking. Moreover, as detailed in section II.C.2.a.iii., above, a 1992 Philip Morris document shows that the views expressed by Philip Morris officials in the 1970's and 1980's are still held by Philip Morris employees.[817]

Moreover, even if Philip Morris had significantly researched other motives for smoking, this could not render Philip Morris' research into the pharmacological motives for smoking irrelevant. Neither FDA nor the courts have suggested that a product with pharmacological uses must not have any other uses if it is to be regulated as a drug or device. When it has been established that a manufacturer intends that its product be used for a pharmacological purpose, FDA's jurisdiction is not defeated by a showing that the

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[816] *Id.* at H7682.

See also Dunn WL (Philip Morris Inc.), *Plans and Objectives–1979* (Dec. 6, 1978) ("All of the effort of the Behavioral Research Laboratory is aimed at achieving this objective: To understand the psychological reward the smoker gets from smoking, to understand the psychophysiology underlying this reward, and to relate this reward to the constituents in smoke"), in 141 Cong. Rec. H7668–7670 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

Dunn WL (Philip Morris Inc.), *Plans and Objectives–1980* (Jan. 7, 1980), in 141 Cong. Rec. H7670–7672 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[817] Philip Morris Inc., Draft Report Regarding a Proposal for a "Safer" Cigarette, Code-named *Table*. *See* AR (Vol. 531 Ref. 122).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

manufacturer also intends the product to be used for other, nonpharmacological purposes. *See, e.g., United States v. Guardian Chemical Corp.*, 410 F.2d 157, 162-163 (2d Cir. 1969) (solvent intended both to dissolve kidney stones and to clean medical instruments was properly regulated as a "drug"). Thus, if there is evidence that nicotine-containing tobacco products are intended to produce significant drug effects in consumers, the fact that manufacturers may also intend them to provide "flavor" or other nonpharmacological effects would not defeat a finding that such products are "drugs" within the meaning of the Act.

2. Philip Morris also contends that in reproducing certain quotes from Philip Morris documents, FDA omitted portions of the documents that would have shown that the author did not believe that people smoke to obtain the pharmacological effects of nicotine. Philip Morris cites four examples. FDA has reviewed each of the documents in question and has concluded that each of the statements quoted in the Jurisdictional Analysis has been fairly presented and has not been taken out of context.

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First, FDA reproduced in the Jurisdictional Analysis a number of quotes from memoranda, presentations, and letters by William Dunn, a senior scientist at Philip Morris, who was responsible for a large number of research projects on smoking motivation. The quotes demonstrated that Dunn believed people smoke to obtain the pharmacological effects of nicotine. *See* 60 FR 41591, 41596–41599, 41682, 41756, 41761. Philip Morris claims that several quotes were taken out of context, and that the full context demonstrates that Dunn did not believe the pharmacological effects of nicotine are the primary reason people smoke, and in fact did not know why people smoke. Philip Morris

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

also contends that the quotes attributed to Dunn were in fact the views of other scientists that Dunn was simply describing.

The collected writings of William Dunn could not be clearer. As is fully demonstrated in the Jurisdictional Analysis, he made repeated statements throughout his career reflecting a consistent belief that people smoke primarily to obtain the psychopharmacological effects of nicotine. As recently as 1994, when Dunn was visited by FDA investigators, he told them that people smoke for the nicotine.[818] At a conference in 1972, Dunn explained his "conviction" that consumers smoke for the pharmacological effects of nicotine. This quote also refutes Philip Morris' claim that Dunn was merely describing the views of other scientists:

> Let me explain *my conviction.*
>
> *The cigarette should be conceived not as a product but as a package. The product is nicotine.* The cigarette is but one of many package layers . . . . *The smoker must strip off all these package layers to get to that which he seeks* . . . . Think of the cigarette pack as a storage container for a day's supply of nicotine . . . . Think of the cigarette as a dispenser for a dose unit of nicotine . . . . Think of a puff of smoke as the vehicle of nicotine:
>
> 1) A convenient 35 cc mouthful contains approximately the right amount of nicotine
> 2) The smoker has wide latitude in further calibration: puff volume, puff interval, depth and duration of inhalation . . .
> 3) Highly absorbable: 97% nicotine retention
> 4) Rapid transfer: nicotine delivered to blood stream in 1 to 3 minutes . . . .
>
> Smoke is beyond question the most optimized vehicle of nicotine.[819]

[818] *See* notes summarizing May 10, 1994 meeting between FDA and Dunn WL. *See* AR (Vol. 21 Ref. 231).

[819] Dunn WL (Philip Morris Inc.), *Motives and Incentives in Cigarette Smoking* (1972), at 5-6 (emphasis added). *See* AR (Vol. 12 Ref. 133).

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Dunn further explained how he and other Philip Morris officials could both express uncertainty about "why people smoke" and believe that they smoke for the pharmacological effects of nicotine: "If we accept the premise that nicotine is what the smoker seeks, we've still not answered the question 'Why do people smoke'? We've merely reformulated it to read 'Why does the smoker take nicotine into his system?'"[820]

Thus, it was Dunn's "conviction" that people smoke to obtain a systemic dose of nicotine. What remained to be determined was precisely why the pharmacological effects of nicotine were reinforcing to smokers and what biochemical mechanisms were triggered by nicotine in the central nervous system. In fact, the records of Philip Morris research between the 1960's and the 1980's demonstrate that Philip Morris spent those decades conducting exhaustive research to determine the physiological and psychoactive effects of nicotine inhalation that cause smokers to repeatedly seek nicotine, and to ascertain the "dose-regulating" mechanisms through which smokers obtain an adequate amount of nicotine to achieve those effects.[821] *See* Jurisdictional Analysis, 60 FR 41599.

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Accordingly, FDA concludes that it has appropriately represented the words of William Dunn.

The second document is a 1969 speech to the board of directors of Philip Morris by Helmut Wakeham, vice president for research and development. The speech begins with the statement that scientists cannot yet give a definitive explanation of why people smoke "backed up by fact." The speech nevertheless attempts to answer the question by

[820] *Id.* at 6-7.

[821] *See* documents printed in 141 Cong. Rec. H7646–7683 (daily ed. Jul. 25, 1995), and 141 Cong. Rec. H8127–8135 (daily ed. Aug. 1, 1995). *See* AR (Vol. 14 Ref. 175a and Vol. 711 Ref. 6).

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marshaling three types of available evidence: what smokers say about why they smoke, what differences in personality characterize smokers and nonsmokers, and what the "immediate effects of smoke inhalation upon . . . human body function" are.[822] In the latter category, the speech provides a long list of nicotine's effects on human body function, including "arousal center in brain stem excited."[823] Following this discussion of the evidence, the speech concludes with the quote cited by FDA in the Jurisdictional Analysis: "We are of the conviction, in view of the foregoing, that the ultimate explanation for the perpetuated cigaret habit resides in the pharmacological effect of smoke upon the body of the smoker, the effect being most rewarding to the individual under stress."[824]

This document speaks for itself. It is beyond question that the quoted statement reflects the "conviction" of the author of the speech that people continue to smoke to obtain the pharmacological effects of nicotine, and that this conviction existed as a result of the available data.

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The third document cited by Philip Morris provides equally weak support for the claim that Philip Morris researchers were uncertain whether people smoke to obtain nicotine. From an internal Philip Morris document entitled "Why People Start to Smoke," FDA printed a quote from the end of the document describing the results of a "special

[822] Wakeham H (Philip Morris Inc.), *Smoker Psychology Research* (Nov. 26, 1969), at 9. *See* AR (Vol. 11 Ref. 142).

[823] *Id.* at 10.

[824] *Id.* at 11.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

study done for Philip Morris" on "the motivation that leads to a *continuation* of smoking".[825]

> [T]he circumstances in which smoking occurs may be generalized as follows:
>
> 1. As a narcotic, tranquilizer, or sedative. Smokers regularly cigarettes at times of stress.
> 2. At the beginning or ending of a basic activity. . . .
> 3. Automatic smoking behavior.[826]

Philip Morris points to a statement, from the portion of the document on why people *start* smoking, that "[t]here are surprisingly few hard facts on the question of the *initiation* of smoking,"[827] claiming that this somehow shows that the author is unsure of why people *continue* to smoke. As the document itself demonstrates, the author describes no uncertainty on the question of why people continue to smoke.

The fourth document cited by Philip Morris is the first of several Philip Morris reports on research conducted by the company to test its hypothesis that smoking is used in times of stress as an "anxiety reducer."[828] The proposed study involved administering shocks to college students and determining whether stress caused the students to smoke more. According to Philip Morris, the research proposal expresses uncertainty about whether smoking mitigates stress, and therefore cannot support FDA's conclusion that Philip Morris officials believed that nicotine's pharmacological effects motivate smoking behavior.

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[825] Udow A (Philip Morris Inc.), *Why People Start to Smoke* (Jun. 2, 1976), in 141 Cong. Rec. H7663-H7664 (daily ed. Jul. 25, 1995) (emphasis added). *See* AR (Vol. 14 Ref. 175a).

[826] *Id.* at H7664.

[827] *Id.* at H7663 (emphasis added).

[828] Ryan FJ (Philip Morris Inc.), *Proposed Research Project: Smoking and Anxiety* (Dec. 23, 1969), in 141 Cong. Rec. H7648 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

FDA disagrees that this document can be used to demonstrate that Philip Morris is uncertain about the relationship of smoking and stress. Because the document in question merely proposes the research to test the hypothesis that smoking reduces anxiety, it does not attempt to answer the question posed. What Philip Morris fails to point out is that this research, once begun, showed a "very high" correlation between personality factors, "particularly the Anxiety factor," and puff rate and that the researchers were "very much encouraged by the trend of these findings."[829] In fact, this study design appears to have been abandoned in favor of other designs only because "fear of shock is scaring away some of our more valuable subjects."[830] Subsequent research reports show that Philip Morris researchers continued to obtain results showing a correlation between anxiety and both puffing and nicotine intake,[831] and subsequent statements by Philip Morris researchers continue to show that they believed that one of the primary motives for smoking is to relieve stress.[832]

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[829] Dunn WL (Philip Morris Inc.), *Consumer Psychology* (Sep.16-Oct. 15,1971) (discussing projects entitled, "Shock I, II, III, IV"), in 141 Cong. Rec. H7648-7649 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[830] Dunn WL (Philip Morris Inc.), *Quarterly Report-Projects 1600 and 2302* (Oct. 5, 1972) in 141 Cong. Rec. H7649 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[831] Dunn WL (Philip Morris Inc.), *1600 Objectives for 1973* (Nov. 14, 1972) (subjects show differential heart rate when threatened with shock on days when they are allowed to smoke compared to days when they are not), in 141 Cong. Rec. H8130 (daily ed. Aug. 1, 1995) *See* AR (Vol. 711 Ref. 6).

Philip Morris Research Center. *Behavioral Research Annual Report* (Jul. 18, 1975), in 141 Cong. Rec. H7652, H7654 (daily ed. Jul. 25, 1995). *See* AR (Vol. 21 Ref. 240a-2).

[832] Udow A (Philip Morris Inc.), *Why People Start to Smoke* (Jun. 2, 1976) ("the circumstances in which smoking occurs may be generalized as follows: 1. As a narcotic, tranquilizer, or sedative. Smokers regularly use cigarettes at times of stress. . . ."), in 141 Cong. Rec. H7664 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

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Not only do the documents discussed immediately above contradict Philip Morris' assertion that its employees do not know why people smoke, but the available Philip Morris documents contain overwhelming support for the finding that Philip Morris officials believe that the major reason people smoke is to obtain the pharmacological effects of nicotine. Expressions of this belief are repeated frequently and consistently over the period of years reflected in these documents. *See, e.g.*, Jurisdictional Analysis, 60 FR 41595–41599, 41608, 41613–41615, 41650–41652.

3. Philip Morris contends that in reproducing William Dunn's statement of his "conviction" that cigarettes are the "most optimized vehicle" for delivering nicotine, *see* comment 2, above, FDA omitted a subsequent paragraph in which the scientist attempted to defuse concern about his "drug-like conceptualization of the cigarette":

> Lest anyone be made unduly apprehensive about this drug-like conceptualization of the cigarette, let me hasten to point out that there are many other vehicles of sought-after agents which dispense in dose units: wine is the vehicle and dispenser of alcohol, tea and coffee are the vehicles and dispensers of caffeine, matches dispense dose units of heat, and money is the storage container, vehicle and dose-dispenser of many things.[833]

Philip Morris claims that this paragraph demonstrates that the earlier part of the quote cannot be used as evidence that Philip Morris intends cigarettes as nicotine delivery systems.

FDA disagrees. The paragraph quoted by Philip Morris illustrates that tobacco company officials were aware of the potential consequences of admitting that cigarettes are "drug-like." Moreover, the paragraph does not in any way undercut the fundamental

[833] Dunn WL (Philip Morris Inc.), *Motives and Incentives in Cigarette Smoking* (1972), at 6. *See* AR (Vol. 12,Ref. 133).

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point made by Dunn: that cigarettes are *nicotine* delivery systems. The fact that other items can also be conceptualized as delivery systems for various things cannot alter what it was that Dunn believed was the essential ingredient delivered by cigarettes: *doses of nicotine*. He did not conceptualize cigarettes as delivery systems for flavor, or taste, or something to occupy one's hands. Rather, he conceptualized cigarettes as delivery systems for "a dose unit of nicotine," which is "delivered to [the] blood stream in 1 to 3 minutes."[834]

4. Philip Morris also contends that in reproducing certain quotes from Philip Morris documents, FDA omitted portions of the documents that were inconsistent with the quoted portion.

First, Philip Morris contends that FDA omitted a significant passage from a quote on a proposed Philip Morris study on smoking and hyperactivity. The full quote with the omitted passages follows:

> Some children are so active (or "hyperkinetic") that they are unable to sit quietly in school and concentrate on what is being taught. In recent years it has been found that amphetamines, which are strong stimulants, have the anomalous effect of quieting these children down and enabling them to concentrate in the face of distractions which otherwise would have disrupted their attention. Many children are therefore regularly administered amphetamines throughout grade school years. The wisdom of such prescription is open to question and some published reports have suggested that caffeine, in the form of coffee or tea for breakfast would produce the same end result. We wonder whether such children may not eventually become cigarette smokers in their teenage years as they discover the advantage of self-stimulation via nicotine. We have already collaborated with a local school system in identifying some such children presently in the third grade; we are reviewing the available literature on the topic; and we may propose a prospective study of this relationship. It would be good to show that smoking is an advantage to at least one

[834] *Id.* at 5-6.

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subgroup of the population. Needless to say, we will not propose giving cigarettes to children.[835]

The full quote demonstrates that Philip Morris researchers regarded nicotine as a stimulant and proposed to study whether hyperactive youths use cigarettes, not for flavor or taste, but to self-medicate an attentional disorder. It is completely consistent with FDA's finding that Philip Morris officials believe that nicotine in cigarettes has pharmacological effects and that consumers use cigarettes to obtain those effects.

Philip Morris claims that the researchers were equating nicotine and caffeine. It is clear from this and later references to this study that Philip Morris was interested in whether nicotine is used to self-medicate hyperactivity by smokers who as children were "known to have their hyperactive or impulsive behaviors reduced by drugs (e.g., Ritalin)."[836] If the researchers equated nicotine and caffeine, they regarded both substances as stimulant drugs that could be used to treat hyperactivity through their pharmacological effects. It is unlikely that they did equate them, however, since the same researchers had 2 years earlier demonstrated that nicotine produces a much more pronounced stimulant effect than caffeine.[837]

Philip Morris also claims that this document proposed a study on hyperkinetic adults, rather than children. Nothing in the available documents supports this claim. The documents mention only a study of hyperkinetic "children," whom Philip Morris

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[835] Dunn WL (Philip Morris Inc.), *Smoker Psychology/May 1-31, 1974* (Jun. 10, 1974), in 141 Cong. Rec. H7651 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[836] Dunn WL (Philip Morris Inc.), *Smoker Psychology/April 1-30, 1977* (May 13, 1977), in 141 Cong. Rec. H7657 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[837] Memorandum from Schori TR to Dunn WL, *Smoking and Caffeine: A Comparison of Physiological Arousal Effects* (May 17, 1992), at 1-2. *See* AR (Vol. 15 Ref. 189-7).

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researchers propose to identify and follow to establish whether they become smokers in their "teenage years."

Second, Philip Morris contends that the context of a statement made by Helmut Wakeham that "nicotine is believed essential to cigarette acceptability" refers to its role in taste and flavor.[838] The full text of this document contradicts Philip Morris' argument. As explained in the Jurisdictional Analysis, 60 FR 41595, earlier in Wakeham's presentation, he described the pharmacological effects of nicotine on smokers:

> (a) Low nicotine doses stimulate, but high doses depress functions.
> (b) Continued usage develops tolerance. . . .
> In contrast to those effects, it is also recognised that smoking produces pleasurable reactions or tranquility, and that this is due at least in part to nicotine, and not entirely to the physical manipulations involved in smoking.[839]

Three pages later, under the heading "Controlled Nicotine in Filler and Smoker," Wakeham says:

> Even though nicotine is believed essential to cigarette acceptability, a reduction in level may be desirable for medical reasons.
>
> Problems:
>
> 1. How much nicotine reduction will be acceptable to the smoker?
> 2. What taste difference will be tolerated?[840]

The document, on its face, demonstrates two things: (1) Wakeham believed that nicotine produced pharmacological effects in smokers; and (2) the problem of determining

[838] Wakeham H (Philip Morris Inc.), *Tobacco and Health–R&D Approach* (Nov. 15, 1961), at 43. *See* AR (Vol. 125 Ref. 1314).

[839] *Id.* at 40.

[840] *Id.* at 43.

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the level of nicotine reduction that would be "acceptable to the smoker" is separate from the problem of determining what taste difference would be tolerated. Had Wakeham believed that nicotine is essential only for taste, only the second question would have been relevent. Instead, he recognized that a reduction in nicotine would not be acceptable to smokers for the additional reasons he had already spelled out: that nicotine produces mood-altering reactions that smokers seek. The plain language of the document thus fails to substantiate Philip Morris' claim that Wakeham believed that nicotine is essential only for taste. As in many other tobacco company documents, nicotine's role in taste, if it is mentioned at all, is seen as secondary to its pharmacological role. *See* Jurisdictional Analysis, 60 FR 41772–41778.

5. Philip Morris argues that some of the statements cited by FDA were only Philip Morris researchers' "premises" and "working hypotheses" or even the hypotheses of outside researchers. According to Philip Morris, these statements are not "facts" or conclusions based on data and are therefore irrelevant to intended use.

FDA disagrees that these consistent statements of Philip Morris researchers that people smoke to obtain the pharmacological effects of nicotine are irrelevant to Philip Morris' intent in manufacturing and marketing cigarettes. In establishing the intended use of Philip Morris' tobacco products, the premises, hypotheses, and beliefs of the scientists whose job within the company is to understand the motives for smoking, and who regularly communicate those views to company executives, are highly relevant. Philip Morris and other tobacco companies contend that cigarettes are labeled for "pleasure," not pharmacological effects, and that nicotine is present in cigarettes only for flavor. On this basis, the company argues that cigarettes are not intended as drugs or devices. Nowhere,

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however, in the publicly available Philip Morris documents, or in the documents produced by Philip Morris in this proceeding, do their scientists put forward a premise or hypothesis that people smoke primarily for nicotine's flavor and/or any other nonpharmacological motive—much less communicate such a view to company executives. The evidence in the administrative record demonstrates, instead, that during the entire period covered by those documents, Philip Morris scientists were communicating to their superiors their scientific opinion that nicotine's pharmacological effects are the primary motivator of smoking behavior.

6. Philip Morris also argues that its researchers' "hypotheses" were not ultimately supported by the results of their research.

FDA disagrees that the documents show that the major premises of Philip Morris scientists concerning the role of nicotine in tobacco use were disproven. These premises center on the scientists' often stated belief that cigarette smoking is reinforced by the pharmacological effects of nicotine on the brain. In fact, this premise continued to be repeated and even strengthened over the period of research reflected in the documents. For example, the major premise of a 1974 research report is that "the smoking habit is maintained by the reinforcing effects of the pharmacologically active components of smoke. A corollary to this premise is that the smoker will regulate his smoke intake so as to achieve his habitual quota of the pharmacological action."[841]

Philip Morris attempts to use this research report in support of its claim that Philip Morris scientists failed to find support for their beliefs that people smoke to obtain the

[841] Philip Morris Research Center, *Behavioral Research Annual Report, Part II* (Nov. 1, 1974) (approved by Osdene TS), in 141 Cong. Rec. H7658, H7660 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

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pharmacological effects of nicotine. According to Philip Morris, this report refuted the compensation theory.[842] Philip Morris' claim that its researchers refuted their major premises fails on two grounds. First, the document shows that Philip Morris researchers considered the compensation theory to be at most a "corollary" of their major premise that smoking is maintained by the reinforcing effects of nicotine. Philip Morris makes no attempt to show that the major premise was disproven. Nor could it. Philip Morris conducted one of the earliest definitive studies on nicotine's reinforcing effects in the early 1980's, well before similar research had been published by outside scientists. As William Dunn told T.S. Osdene, Philip Morris' director of research, the company's research made "it quite clear that nicotine can function as a positive reinforcer for rats."[843] As described in section II.A.3.c.i., above, the ability of a substance to function as a "positive reinforcer" in animals is one of the most telling pieces of evidence that the substance will be addictive in humans.

Second, both the 1974 and subsequent research reports (through and including the last available report in 1980) show that Philip Morris continued to believe in, and test, the compensation theory, using ever more sophisticated and precise methods. Philip Morris relies on a statement from the 1974 report in which the researchers note that previous attempts to show compensation by analyzing the number and amount of cigarettes smoked had shown positive trends but not convincing evidence that the smoker regulates intake of

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[842] "Compensation," as described in section II.A.7.i., above, describes the behavior of smokers who are given cigarettes with more or less nicotine than their usual brands. Data, including tobacco industry data, show that smokers "compensate" by altering their smoking behavior (e.g., by smoking more cigarettes or smoking each cigarette more intensely) to obtain their customary nicotine intake.

[843] Dunn WL (Philip Morris Inc.), *Plans and Objectives–1981* (Nov. 26, 1980), in 141 Cong. Rec. H7681-7682 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

nicotine. Philip Morris omits subsequent statements demonstrating that the researchers have not "refuted" the compensation theory, but have merely decided to take a new approach to establishing compensation. Following the statement quoted by Philip Morris, the researchers state that they "question whether the indices of intake which have been investigated to date are, in fact, the appropriate indices to be measuring."[844] Instead, they believe that new evidence suggests that compensation may be accomplished through the inhalation patterns of smokers:

> [O]bservations [concerning differences in how smoke is inhaled from smoker to smoker] have made us aware of a heretofore unnoticed *mechanism* that has the potential of affording the smoker a wide latitude of control over the amount of smoke he brings into contact with the absorption sites.[845]

The researchers go on to describe a new series of experiments designed "to systematically observe the inhalation patterns of smokers" and thereby determine whether compensation for nicotine is occurring.[846] The researchers also developed, three years later, a new theoretical model to explain their inability up to that point to demonstrate compensation. Under this theory, some smoking is triggered by "deficits or surfeits of nicotine (or some unknown smoke components)" and some by external stimuli:

> The adoption of this point of view by members of the staff will lead us to recognize that apparent failures of [the] nicotine compensation model may not in fact be failures at all and that *nicotine compensation is a real phenomenon which is masked by the fact that smokers smoke many cigarettes out of habit rather than need.*[847]

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[844] Philip Morris Research Center, *Behavioral Research Annual Report, Part II* (Nov. 1, 1994), in 141 Cong. Rec. H7658, 7660 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[845] *Id.*

[846] *Id.*

[847] Dunn WL (Philip Morris Inc.), *Behavioral Research Accomplishments--1977* (Dec. 19, 1977), in 141 Cong. Rec. H7666-7667 (daily ed. Jul. 25, 1995) (emphasis added). *See* AR (Vol. 14 Ref. 175a).

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The Philip Morris research reports demonstrate that Philip Morris continued to attempt to measure inhalation patterns throughout the period covered by the reports, and that the researchers continued to believe, and sometimes showed, that smokers compensate for nicotine.[848]

Finally, Philip Morris cites a small number of minor studies in the Philip Morris research documents in which the researchers did not find discernible effects due to smoking; it claims that these show that Philip Morris failed to find support for the belief that nicotine's pharmacological effects motivate smoking. The apparent failure of a small fraction of its studies to demonstrate particular pharmacological effects from nicotine cannot obscure what is evident from a fair reading of the publicly available research reports: the company's research on nicotine demonstrated that nicotine had many significant pharmacological effects on smokers. The record also shows that, through the period covered by the reports, Philip Morris' emphasis on the pharmacological motivations for smoking increased and its research on the pharmacological effects of nicotine grew in size and sophistication. By the end of that period, Philip Morris had successfully established that nicotine is a positive reinforcer in rats, that it produces psychoactive effects like other drugs of abuse, that it produces tolerance, and that it acts

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[848] *See, e.g.*, Letter from Dunn WL to Schachter S (Sep. 8, 1975) (Philip Morris expects inhalation patterns "to be dose-regulating mechanisms of remarkable precision and sensitivity"), in 141 Cong. Rec. H7662 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

Dunn WL (Philip Morris Inc.), *Behavioral Research Accomplishments–1977* (Dec. 19, 1977) ("We have . . . [s]hown that we can distinguish between [nicotine] regulator and nonregulator smokers and that after being deprived, the regulators do indeed try to make up for lost intake"), in 141 Cong. Rec. H7666 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

Dunn WL (Philip Morris Inc.), *Plans and Objectives–1981* (Nov. 26, 1980), in 141 Cong. Rec. H7681, H7683 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

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centrally in the brain. These are the standard animal tests performed by pharmaceutical companies and public health organizations to establish that a substance is addictive. At this time, Philip Morris was also engaged in a broad-based study of the effects of smoking and nicotine on *human* brain wave patterns to "identify as far as possible the neural elements which mediate cigarette smoking's reinforcing actions."[849] The record thus contradicts Philip Morris' claim that its research failed to bear out the premise that people smoke to obtain nicotine.

7. Philip Morris argues that FDA has mischaracterized statements of Philip Morris officials in several company documents related to the addictive effects of nicotine and cigarettes. FDA has reviewed the statements and concluded that it has not mischaracterized the statements that it relied on.

First, in the Jurisdictional Analysis, 60 FR 41607–41608, FDA cited a Philip Morris study on a smoking cessation campaign in Greenfield, Iowa, in 1969 as evidence that Philip Morris researchers recognized that smoking cessation produces a withdrawal syndrome. Philip Morris claims that its study did not conclude that nicotine is "addictive" and that the study showed only that former smokers experienced "transient . . . common behavioral mannerisms such as eating more, tapping their fingers, twiddling their thumbs, biting their lips, chewing on matches, or feeling ill-tempered."[850] Philip Morris also argues that this study was published more than 20 years ago and therefore is not "new" evidence.

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[849] *Id.* at H7681.

[850] Philip Morris Inc., Comment (Jan. 2, 1996), at 17. *See* AR (Vol. 519 Ref. 105).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

FDA believes that the Philip Morris study on the Iowa "cold turkey" campaign provides solid evidence that Philip Morris knows that abstinence from smoking produces a significant, long-term withdrawal syndrome. As discussed in section II.A.3., above, withdrawal is recognized as one of the characteristic features of drug dependence. Contrary to the comment's claim that the study revealed only mild and "transient" symptoms, the study author, a Philip Morris researcher, summarizes the symptoms of those who quit smoking this way:

> Even after *eight months* quitters were apt to report having neurotic symptoms, such as feeling depressed, being restless and tense, being ill-tempered, having loss of energy, being apt to doze off, etc. They were further troubled by constipation and weight gains which averaged about 5 lbs. per quitter.[851]

The researcher later reports on the worsening of health symptoms among the quitters, observing that their "list of complaints is long and impressive."[852] The author encapsulates the quitters' experience as follows:

> This is not the happy picture painted by the Cancer Society's anti-smoking commercial which shows an exuberant couple leaping in the air and kicking their heels with joy because they've kicked the habit. A more appropriate commercial would show *a restless, nervous, constipated husband bickering viciously with his bitchy wife who is nagging him about his slothful behavior and growing waistline.*[853]

Accordingly, this study provides evidence that Philip Morris knows that smokers suffer significant, long-term withdrawal symptoms, a characteristic feature of addictive

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[851] Ryan FJ (Philip Morris Inc.), *Bird-1: A Study of the Quit-Smoking Campaign in Greenfield, Iowa, in Conjunction with Movie, Cold Turkey* (Mar. 1971), at 1. (emphasis added). *See* AR (Vol. 390 Ref. 6394).

[852] *Id.* at 31.

[853] *Id.* at 33 (emphasis added).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

substances. There is no support for Philip Morris' contention that the withdrawal symptoms reported in this study are not comparable to withdrawal symptoms from other drugs that produce physical dependence. The withdrawal symptoms reported by Philip Morris include many of the same changes in mood, behavior, and physical functioning identified as evidence of a withdrawal syndrome for all drugs that produce physical dependence. They are the same symptoms that have been recognized by the Surgeon General and other public health organizations as evidence that nicotine produces a withdrawal syndrome and physical dependence.[854]

Finally, Philip Morris' claim that this study was published 20 years ago is misleading. The material quoted in the Jurisdictional Analysis and here comes principally from an internal Philip Morris study report that was not published.[855] Another version of the study was published, in which the quoted material was omitted.[856]

Philip Morris also argues that FDA "deliberately mischaracterize[d]" another Philip Morris document in which Philip Morris acknowledges both nicotine dependence and a withdrawal syndrome from cigarette deprivation. FDA notes that Philip Morris challenges only the use of the statement to show that Philip Morris acknowledges withdrawal; Philip Morris makes no claim that this statement does not acknowledge nicotine dependence.

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[854] Surgeon General's Report, 1988, at 198-221. *See* AR (Vol. 129 Ref. 1592).

American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 244. *See* AR (Vol. 5 Ref. 46-1).

[855] Ryan FJ (Philip Morris Inc.), *Bird-1: A Study of the Quit-Smoking Campaign in Greenfield, Iowa, in Conjunction with Movie, Cold Turkey* (Mar. 1971). *See* AR (Vol. 21 Ref. 207).

[856] Ryan FJ (Philip Morris Inc.), Cold turkey in Greenfield, Iowa: a follow-up study, in *Smoking Behavior: Motives and Incentives*, ed. Dunn WL (Washington DC: VH Winston & Sons, 1973). *See* AR (Vol. 8 Ref. 105).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

The document is a report from W. L. Dunn to T. S. Osdene, vice president for research and development, entitled, "Plans and Objectives--1980." In describing the company's "Experimental Psychology Program," the report states that the first objective of the program is to "gain better understanding of the role of nicotine in smoking." The report describes one of its approaches to this objective as follows:

> Identification of two smoking population subgroups, one of which has greater nicotine needs than the other. We have described these people in the past as compensators and noncompensators, and attempted to define them by their consumption changes when nicotine deliveries were moderately shifted. However, we've had no great success in the identification to date. Now we may have two extra tools to use: Commercial PM cigarettes of ultra low tar and nicotine, and salivary nicotine concentrations. Others, principally at Columbia University, have suggested that shifts to ultra low nicotine cigarettes produce the same type of psychological stress behaviors as quitting. *We therefore propose a shift study in which smokers are shifted to an ultra low brand, and the key dependent variable becomes the presence or absence of the withdrawal syndrome. Those who show evidence of nicotine dependence and those who do not can then be used to test our hypotheses on the relationship of salivary concentration to smoking behavior.*[857]

Philip Morris claims that this statement contains no acknowledgment of a cigarette withdrawal syndrome, because the Philip Morris researchers: (1) found no support for their hypothesis that people compensate for changes in nicotine yield; (2) were merely testing hypotheses proposed by outside researchers; and (3) were referring to psychological stress behaviors, not physiological symptoms when they spoke of withdrawal.

The full text of this statement fails to support Philip Morris' strained construction. The obvious purpose of the statement is to explain that the researchers intended to try a

[857] Dunn WL (Philip Morris Inc.), *Plans and Objectives--1980* (Jan. 7, 1980), in 141 Cong. Rec. H7670, H7672 (daily ed. Jul. 25, 1995) (emphasis added). *See* AR (Vol. 14 Ref. 175a).

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new approach to identifying "compensators" and "noncompensators," relying on evidence of withdrawal/dependence. The researchers are clear that withdrawal is an established syndrome they will use to identify compensators and noncompensators, not the reverse. The only outside hypothesis mentioned in the statement is the notion that switching to ultra-low nicotine cigarettes can be used to induce the same stress behaviors as quitting. The more fundamental notion that quitting produces a withdrawal syndrome is not an outsider's hypothesis but a clearly accepted premise of the entire approach. Nothing in the statement suggests that the researchers intend to test an "hypothesis" that quitting produces withdrawal; they intend to use this accepted fact to search for compensators and noncompensators. Finally, there is no evidence in the document to support Philip Morris' assertion that the Philip Morris researchers were referring to psychological stress behaviors, not physiological symptoms.

Philip Morris also contends that FDA inappropriately characterized a Philip Morris memo, which FDA briefly cited in a footnote to the Jurisdictional Analysis, as indicating that people smoke to avoid "withdrawal." According to Philip Morris, the memo merely placed cigarettes in the same category as alcohol, tea, coffee, chewing gum, overeating, and sex.

Philip Morris' characterization focuses on the introduction of the memo, while ignoring its central purpose. The actual purpose of the memo is to propose to study the question of why people continue to smoke despite "compelling pressures upon the smoker to discontinue the behavior" and to "document the penalties imposed by discontinuation of

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cigarette smoking."[858] The memo offers the following rationale for documenting the "penalties" of discontinuation:

> The literature on the subject cites body weight gains up to twenty pounds. Constipation has been cited as another sequelae (Ejrup, 1965), as well as blisters in the mouth. Chessick (1964) has warned against the "neurovegetative disequilibrium" that can result and Masoni (1963) contends that some may not be able to stabilize emotionally. There is anecdotal and lay observation of lowered efficiency and heightened irritability upon withdrawal. We know, too, that in periods of non-voluntary deprivation, as in concentration camps of World War II, the incentive value of the cigarette exceeds that of essential foodstuff.[859]

The actual text of the memo thus demonstrates clearly that Philip Morris has knowledge of significant withdrawal symptoms associated with smoking deprivation. The memo displays no skepticism about the existence of the cited withdrawal symptoms.

8. Philip Morris argues that reports of animal research conducted in its laboratories by Philip Morris researchers Victor DeNoble and Paul Mele do not conclude that nicotine is addictive.

The reports in question showed that Philip Morris had established that nicotine functions as a "positive reinforcer" in rats (causes them to seek repeated doses), and has other psychoactive effects characteristic of addictive substances. *See* Jurisdictional Analysis, 60 FR 41754–41758. These reports also showed that Philip Morris conducted research to find nicotine analogues (substitutes) that would have equal or greater reinforcing and psychoactive effects as nicotine. *Id.* These central nervous system effects were characterized by Philip Morris as "desirable properties" of nicotine that could be

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[858] Dunn WL (Philip Morris Inc.), *Stating the Risk Study Problem* (Jul. 29, 1969), at 3. *See* AR (Vol. 15 Ref. 189-6).

[859] *Id.*

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"enhanced" as a result of nicotine analogue research.[860] Finally, these research reports showed that Philip Morris conducted research to find an "optimum" combination of nicotine and acetaldehyde (another component of smoke) that had "maximal reinforcing effects."[861]

FDA disagrees that it inappropriately relied on these studies. FDA did not cite these documents for the proposition that Philip Morris acknowledged that nicotine is addictive. FDA cited them, appropriately, as evidence that Philip Morris: (1) had conducted research demonstrating that nicotine is a positive reinforcer, one of the characteristic features of addictive substances; and (2) understood that the pharmacological effects of nicotine were essential to the market for tobacco products and intended to offer products that affect the central nervous system. *See* Jurisdictional Analysis, 60 FR 41750–41762.

9. Philip Morris states that, during his tenure at Philip Morris, Victor DeNoble repeatedly advised his colleagues that the fact that a substance has positive reinforcement effects does not mean that the substance is "addictive."

FDA agrees that animal self-administration does not alone demonstrate conclusively that a substance will be addictive in humans. As DeNoble stated in his testimony before Congress, however, "[t]he self-administration study is a classical hallmark to indicate that a solution or drug substance has . . . the potential to be a drug of

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[860] Charles JL (Philip Morris Inc.), *Nicotine Receptor Program–University of Rochester* (Mar. 18, 1980). *See* AR (Vol. 32 Ref. 532).

[861] DeNoble VJ (Philip Morris Inc.), *Project Number 1610 (Behavior Pharmacology) Objectives and Plans 1982-1983* (Jul. 20, 1982), at 2. *See* AR (Vol. 345 Ref. 5443).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

abuse in humans."[862] As described earlier, a drug's abuse liability refers to its potential to cause drug dependence/addiction.

As described in section II.A.3.c., above, a complete screen for abuse liability also includes studies that demonstrate that the drug's reinforcing effects are caused by its actions in the central nervous system, that the drug has psychoactive effects, that the drug produces withdrawal and/or tolerance. Philip Morris research also demonstrated that nicotine has each of these properties.[863] These results distinguish nicotine from such nonaddictive substances as saccharin, which are not psychoactive.

As described in section II.C.2.a.ii., above, corporate executives were informed that Philip Morris' own research predicted that nicotine would be a drug of abuse in humans. A reasonable manufacturer with this information should have foreseen that nicotine was likely to be addictive in humans.

10. Tobacco industry comments challenge the reliability of a report submitted by William A. Farone, director of applied research at Philip Morris from 1976 to 1984, entitled "The Manipulation and Control of Nicotine and Tar in the Design and

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[862] *Regulation of Tobacco Products (Part 2): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*. 103d Cong. 2d Sess. 18 (Apr. 28, 1994) (testimony of Victor J. DeNoble). *See* AR (Vol. 708 Ref. 2).

[863] *See, e.g.*, Dunn WL (Philip Morris Inc.), *Plans and Objectives–1980* (Jan. 7, 1980), in 141 Cong. Rec. H7668, H7669 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

DeNoble VJ (Philip Morris, Inc.) *Nicotine Program–Behavioral Research Laboratory* (Apr. 24, 1980), at 2. *See* AR (Vol. 345 Ref. 5446).

Ryan PJ (Philip Morris Inc.), *[illegible] a Study of the Quit-Smoking Campaign in Greenfield, Iowa, in Conjunction with Movie, Cold Turkey* (Mar. 1971). *See* AR (Vol. 21 Ref. 207).

DeNoble VJ, Mele PC (Philip Morris Inc.), *Development of behavioral tolerance following chronic nicotine administration* (unpublished manuscript). *See* AR (Vol. 346 Ref. 5464).

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Manufacture of Cigarettes: A Scientific Perspective." In this report, Farone describes the beliefs of Philip Morris, and, in some cases the tobacco industry, concerning: the essential role of nicotine in tobacco use; research conducted by the industry on nicotine's pharmacological effects; and techniques used by the industry to reduce tar while maintaining an adequate level of nicotine. Farone bases his report on personal knowledge, as well as company documents and published literature. The tobacco industry argues generally that the information in Farone's report should not be relied upon because: (1) many of his statements about Philip Morris or the industry are not supported by documentary evidence; and (2) Farone left Philip Morris in 1984 and therefore does not have personal knowledge of the current operations of the company.

Other comments argue that Farone's report provides additional factual support for the conclusion that Philip Morris scientists and executives understand and intend that the primary role of nicotine in Philip Morris' products is to provide nicotine's pharmacological effects to consumers. These comments also argue that Victor DeNoble, former research scientist for Philip Morris, has publicly confirmed the accuracy of many of the statements made by Farone. Finally, these comments argue that the reliability of the information provided by Farone, is enhanced by its consistency with the sworn testimony of the former vice president for research and development for Brown & Williamson.

FDA disagrees with the tobacco industry comments that Farone's report is not reliable evidence relevant to establishing the intended use of cigarettes. Farone was a high-ranking manager within Philip Morris, whose responsibilities gave him first-hand knowledge of the information presented in the report. As director of applied research, Farone supervised five research divisions with a total of 150 employees, mostly

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professionals. He reported directly to the vice president for research and development and regularly met with other senior management officials, including the CEO and president of Philip Morris, to discuss Philip Morris activities related to basic and applied research, product and process development, manufacturing, and results of test marketing of new products.[864] He was thus in a position to have personal knowledge of the views and activities of Philip Morris concerning the topics discussed in his report. Thus, the fact that he does not cite documentary evidence to support each statement in the report is irrelevant to the weight to which the report is entitled.[865]

The fact that Farone left Philip Morris in 1984 also provides no basis to consider his report irrelevant. As discussed above in section II.C.2.e., the extensive collection of tobacco company statements relied on by the agency reflects a consistent pattern of tobacco industry views spanning three decades. These statements provide evidence of the long-standing knowledge and beliefs of tobacco company officials that cigarettes are primarily used by consumers for the pharmacological effects of nicotine. Farone's statements about the knowledge, beliefs, and actions of the tobacco industry are entirely consistent with the body of industry statements relied on by the agency, adding to their credibility. Moreover, Farone's statements are consistent with the recent Philip Morris

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[864] Declaration of Uydess II. (Feb. 29, 1996), at 23-24. *See* AR (Vol. 638 Ref. 1).

[865] FDA notes that Philip Morris has submitted two affidavits from current employees which purport to provide, based on the personal knowledge of the affiants, information about the measurement of nicotine levels in reconstituted tobacco. Neither of these affidavits cites any documentary support. Thus, Philip Morris appears to believe that FDA is entitled to rely on information based on personal knowledge. Philip Morris Inc., Comment (Apr. 19, 1996), at appendix 3. *See* AR (Vol. 700 Ref. 226).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

document concerning Project Table,[866] demonstrating that the company's views have not changed since Farone left the company.

11. Tobacco industry comments also challenge specific statements made in Farone's report. FDA addresses those comments that challenge statements cited by the Agency.

The tobacco industry contests Farone's statement that it is widely believed within the tobacco industry that nicotine is the primary reason people smoke. The industry argues that the documents cited by Farone do not support this statement, and that industry evidence shows that consumers do not smoke cigarettes "nearly exclusively" or "solely" for the pharmacological effects of nicotine.[867]

FDA disagrees with these comments. As described above and in sections II.C.6.a.ii. and iii., below, there is ample support, including the documents cited by Farone, for the conclusion that tobacco industry officials believe that people use tobacco primarily to obtain the pharmacological effects of nicotine. Moreover, as discussed above, Farone's position and responsibilities within Philip Morris were such that the statements based on his personal knowledge may be considered reliable evidence. Finally, Farone's statement is corroborated by the existence of dozens of similar statements by Philip Morris officials in other documents cited in section II.C.2.a.i., above, and in the Jurisdictional Analysis. *See* 60 FR 41584–41620.

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[866] Philip Morris, Inc., Draft Report Regarding a Proposal for a "Safer" Cigarette, Code-named *Table*. *See* AR (Vol. 531 Ref. 122).

[867] Philip Morris Inc., Comment (Apr. 19, 1996), at 57. *See* AR (Vol. 700 Ref. 226).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

The tobacco industry comments present no contradictory statements or other evidence to demonstrate that tobacco industry officials do not believe that nicotine is the primary reason people smoke. Instead, the industry argues that there is evidence that, in fact, consumers do not smoke cigarettes "solely" or "nearly exclusively" for the pharmacological effects of nicotine. These comments misconstrue the nature of the evidence required to establish intended use. The statements of Farone and others are properly used by FDA to show that Philip Morris *knows* that consumers use cigarettes for the pharmacological effects of nicotine. This knowledge is relevant to establishing the company's intent to affect the structure and function of the body. See 21 CFR 201.128 and 801.4. In establishing intended use through a manufacturer's actual knowledge, it is not necessary for the Agency to show knowledge that consumers use tobacco nearly exclusively for its pharmacological effects. *Cf. Action on Smoking and Health v. Harris*, 655 F.2d 236, 240 (D.C. Cir. 1980) (FDA must establish nearly exclusive consumer use for pharmacological effects only where there is no other evidence of manufacturer's intent).

Moreover, as described in section II.B., above, the scientific evidence demonstrates that the pharmacological effects of nicotine are the primary motivation for tobacco use, and that other aspects of tobacco use, such as flavor, are secondary. Indeed, the data show that tobacco users enjoy the flavor of tobacco products because they have come to associate its flavor with obtaining the pharmacological effects of nicotine. Thus, contrary to Philip Morris' comment, even though not necessary to establish "intended use," the evidence shows that consumers do use tobacco products nearly exclusively for the pharmacological effects of nicotine.

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Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

ii. Comments on Specific RJR Statements and Research Projects. Like Philip Morris, RJR argues that FDA misused statements and research reports by RJR officials that the Agency relied upon as evidence that RJR officials believe that consumers use cigarettes to obtain the pharmacological effects of nicotine. FDA has reviewed the statements and research reports in context and concluded that, with one minor exception, the Agency correctly relied upon them.

1. RJR argues that the 1972 memorandum by Claude Teague, assistant director for research at RJR,[868] cited by FDA, does not provide evidence of the intended use of cigarettes because Teague was only presenting a "hypothesis" to stimulate discussion, and because the document does not reflect institutional intent. RJR focuses heavily on the fact that one of the quoted paragraphs and a few other phrases in the document begin with "if" or otherwise suggest uncertainty.

At the time the Jurisdictional Analysis was published, two paragraphs from the memorandum that had been published in the *New York Times*. The complete nine-page memorandum was subsequently submitted to the Agency in a comment and is discussed above in section II.C.2.b.i. The full document demonstrates that RJR's assistant vice president for research asserted as fact, not hypothesis, that nicotine's pharmacological effects are the primary reason people smoke and that cigarettes are nicotine delivery systems. Before the paragraph that begins "If nicotine is the *sine qua non* of tobacco products," Teague says:

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[868] Teague CE (R.J. Reynolds Tobacco Co.), *Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of Nicotine Therein* (Apr. 14, 1972), at 1-2. *See* AR (Vol. 531 Ref. 125).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

> Nicotine is known to be a habit-forming alkaloid, hence the confirmed user of tobacco products is primarily seeking the physiological "satisfaction" derived from nicotine—and perhaps other compounds . . . . Thus a tobacco product is, in essence, a vehicle for delivery of nicotine, designed to deliver the nicotine in a generally acceptable and attractive form. Our industry is then based upon design, manufacture and sale of attractive dosage forms of nicotine. . . .[869]

The actual text of the document thus flatly contradicts RJR's claim that Teague was making "suppositions" about nicotine that were "very tentative."[870] He was, instead, stating as established fact that people smoke for the pharmacological effects of nicotine. The later statement, "If nicotine is the *sine qua non* of tobacco," is thus not an "hypothesis" but a rhetorical device to encapsulate the author's previously expressed position.

2. In the Jurisdictional Analysis, FDA relied upon the statements of RJR researchers in published papers that many of the most important effects of smoking cited by smokers as the reasons they smoke are the pharmacological effects of nicotine. RJR argues that none of the papers asserts that the pharmacological effects of nicotine are the most important reason for smoking, and that the papers also refer to the role of nonpharmacological effects in smoking behavior. RJR also contends that these papers do not show that consumers use tobacco nearly exclusively for its pharmacological effects.

FDA disagrees. A fair reading of these studies indicates that the authors view nicotine as playing a far more significant role in smoking motivation than other, nonpharmacological motives.

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[869] *Id.* at 1.

[870] R.J. Reynolds Tobacco Co., Comment (Jan 2, 1996), at 30. *See* AR (Vol. 519 Ref. 103).

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For example, a paper published in 1991 refers to the fact that some smokers report that they smoke to increase their mental alertness, while others smoke to calm their moods; the paper attempts to prove that both sets of motives can be attributed to the effects of nicotine on different hemispheres of the brain.[871] The study demonstrated that smoking produced EEG effects in different hemispheres of the brain, depending on the depth of inhalation, leading the researchers to conclude that "light inhaling . . . smokers may smoke primarily for purposes of mental activation and performance enhancement" while "an important motive for deep inhaling smokers might be anxiety reduction."[872] Nonpharmacological motives for smoking are not mentioned at all. In studies where they are mentioned, RJR researchers never claim that nonpharmacological motives are more important to the smoker than nicotine.

RJR's contention that its published studies do not demonstrate "nearly exclusive consumer use" of cigarettes for pharmacological effects does not diminish their relevance to establishing intended use. These studies were designed by RJR to examine the effects of smoking on the human brain and on behavior, not to quantify consumer use. These studies are properly used by FDA to show that RJR knows that consumers use cigarettes for the pharmacological effects of nicotine. A manufacturer's actual knowledge is relevant to establishing the intended use of these products to affect the structure and function of the body. See 21 CFR 201.128 and 801.4. Moreover, when the evidence of tobacco manufacturer's statements, research, and actions demonstrates that their products are

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[871] Pritchard WS (R.J. Reynolds Tobacco Co.), Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490. *See* AR (Vol. 3 Ref. 23-2).

[872] *Id.* at 488.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

actually intended to affect the structure or function of the body, it is not necessary for the Agency to show that consumers use tobacco nearly exclusively for its pharmacological effects. Some courts have suggested such a showing could be required, but only where there is no other evidence of the intended use and FDA is relying exclusively on actual consumer use. *Action on Smoking and Health v. Harris*, 655 F.2d 236, 240 (D.C. Cir. 1980). The "nearly exclusive" consumer use standard is inapplicable in the context of direct evidence of manufacturers intent. *See* sections II.B.1., above, and II.E.1., below.

3. In the Jurisdictional Analysis, 60 FR 41601, FDA stated that attorneys for RJR had, in a court filing, described the following pharmacological "benefits" of smoking: "satisfaction; stress reduction; relaxation; stimulation; aided concentration; increased memory retention; alleviation of boredom and fatigue; avoidance of loss of vigilance in repetitive and sustained tasks."[873] RJR argues that FDA's use of this litigation response was misleading because: (1) the listed benefits were only those reported by smokers or the literature, and were not subscribed to by RJR; (2) FDA omitted from the quote benefits that were not pharmacological; and (3) the listed benefits were not characterized by RJR as "pharmacological" or "significant," and are likely due to other aspects of smoking, including the sensory aspects. RJR also states that even if some of the benefits quoted by FDA "are in some sense pharmacological," the litigation response is not evidence of intended use.

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[873] Reply to Interrogatories, *Gilboy v. American Tobacco Co. et al.*, No. 314002 (La. Dist. Ct.). *See* AR (Vol. 15 Ref. 194-1). FDA notes that Lorillard has not contested FDA's reliance on a similar court filing by Lorillard in *Covert v. Lorillard et al.*, No. 88-1018-B (M.D.La). *See* AR (Vol. 15 Ref. 194-2).

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II.C.6.

FDA disagrees that its use of the company's statements in litigation was misleading or that the statements fail to provide evidence of intended use. The statement filed in court by RJR was used as evidence that RJR, *speaking as a corporation*, knows that consumers use tobacco for its pharmacological effects. The knowledge of a manufacturer that its product is used for pharmacological effects provides objective evidence of intent to affect the structure and function of the body. The fact that RJR was repeating benefits reported by consumers does not in any way undercut FDA's reliance on the quote: RJR's awareness of how consumers use its product is highly relevant. The fact that the original quote included two nonpharmacological "benefits" of smoking similarly fails to diminish the relevance of the quote. When it has been established that a manufacturer intends that its product be used for a pharmacological purpose, FDA's jurisdiction is not defeated by a showing that the manufacturer also intends the product to be used for other, nonpharmacological purposes. *Guardian Chemical Corp.*, 410 F.2d at 162-163.

Finally, while RJR did not explicitly characterize the benefits as pharmacological in this particular filing, RJR scientists have published reports demonstrating that the company knows that these "benefits" of tobacco are due to the pharmacological effects of nicotine. In one paper, for example, RJR scientists reported on a study whose purpose was to isolate the psychopharmacological effects of nicotine from the effects of other aspects of the cigarette:

> Anxiety relief and improved mental alertness are two of the benefits of smoking commonly reported by smokers as their reason for smoking . . . . [The study results] indicate that *the beneficial effects*

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> *of smoking on cognitive performance . . . are a function of nicotine absorbed from cigarette smoke upon inhalation.*[874]

Thus, RJR scientists characterize the very effects that the corporation listed in the pleading as nicotine's pharmacological effects.

4. RJR challenges FDA's use in the Jurisdictional Analysis of the statement of its former CEO, F. Ross Johnson, in response to a question from a reporter about whether tobacco is addictive: "Of course it's addictive. That's why you smoke the stuff."[875] RJR argues that this statement is not evidence of intent because, as Johnson "explained" in a subsequent letter to the reporter, he used the term "addictive" not in the "technical" sense, but as an expression of the "common experience that some people find it hard to quit smoking, and so continue to smoke."[876] RJR also argues that Johnson's statement should not be attributed to RJR because, at the time he made it, he was no longer employed by RJR, and "there is no indication that Johnson's comment reflected anything he learned or observed" at RJR.[877]

The arguments put forward by RJR for discounting the statement of its former CEO are not persuasive. It is doubtful that the former CEO of a tobacco company would

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[874] Robinson JH, Pritchard WS, Davis RA (R.J. Reynolds Tobacco Co.), Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine, *Psychopharmacology* 1992;108:466-472, at 471 (emphasis added.). *See* AR (Vol. 11 Ref. 129-3).

See also Pritchard WS (R.J. Reynolds Tobacco Co.), Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490 (presenting evidence that both mental alertness and anxiety reduction are a function of nicotine's effects on different parts of the brain). *See* AR (Vol. 3 Ref. 23-1).

[875] Shapiro E, Big spender finds new place to spend, *Wall Street Journal* (Oct. 6, 1994). *See* AR (Vol. 21 Ref. 230).

[876] R.J. Reynolds Tobacco Co., Comment (Jan. 2, 1996), at 21. *See* AR (Vol. 519 Ref. 103).

[877] *Id.*

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

state that tobacco is "addictive" without foreseeing that he would be understood to mean the term in its "technical" sense. The further suggestion that the statement did not reflect Johnson's knowledge while at RJR is similarly unconvincing.

5. RJR argues that FDA incorrectly stated that a particular research article[878] found that tobacco users report "craving." FDA has reviewed the article in question and agrees with the comment that it does not clearly find that smokers report craving.

iii. Comments on Specific Brown & Williamson Statements and Research Projects. In the Jurisdictional Analysis, FDA cited over 75 Brown & Williamson and BATCO documents to demonstrate the cigarette manufacturer's knowledge that cigarettes produce significant pharmacological effects, including causing and sustaining addiction, and are used by smokers for these effects. FDA also cited a substantial number of documents from Brown & Williamson's affiliate, Imperial Tobacco, and from American Tobacco, a company with which Brown & Williamson recently merged. Although Brown & Williamson makes a general assertion that the Agency has mischaracterized these documents, the company makes no attempt to refute FDA's specific characterizations of the vast majority of the Brown & Williamson documents cited by FDA. The Agency believes that these documents speak for themselves and fully support its conclusion that Brown & Williamson intends cigarettes to affect the structure and function of the body.

With respect to the few Brown & Williamson documents regarding nicotine pharmacology that the company does specifically address, FDA has reviewed the company's comments and concludes that the company's statements and research were

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[878] Robinson JH, Pritchard W. The role of nicotine in tobacco use. *Psychopharmacology* 1992;108:395-405. *See* AR (Vol. 14 Ref. 175).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

properly characterized in the Jurisdictional Analysis. These comments and FDA's responses are presented below.

1. FDA relied on a large number of statements from researchers and high-ranking officials of Brown & Williamson and BATCO acknowledging that nicotine is addictive. Brown & Williamson makes a general argument that none of the statements by BATCO employees about addiction is attributable to Brown & Williamson, because their employees were merely reciting language from government and other external sources. The company provides only one example to support this contention. FDA quoted from a speech by Charles Ellis, the science advisor to BATCO's Board of Directors, in which he told an audience of tobacco industry officials: "smoking is a habit of addiction . . . ."[479] According to the comment, Ellis' "terminology mirrored virtually identical phrases used by the Royal College of Physicians three months earlier . . . [and] does not support any conclusion about his own views."[480] Brown & Williamson also makes a baffling argument that the Surgeon General two years later determined that smoking was a "habit" rather than an "addiction" and that the Surgeon General's determination "clearly trumps the earlier imprecise language quoted by FDA."

FDA has reviewed the full text of Ellis' speech and finds no support for Brown & Williamson's contention that Ellis was merely reciting the views of the Royal College; in the quoted passage, Ellis is clearly stating his own views. FDA is similarly unable to conclude that the 1964 determination of the U.S. Surgeon General transformed Ellis' assertion two years

[479] Ellis C (BATCO), The smoking and health problem, in *Smoking and Health–Policy on Research*, Research Conference, Southampton, England (1962), at 4. *See* AR (Vol. 21 Ref. 220).

[480] Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 27. *See* AR (Vol. 529 Ref. 104).

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earlier that "smoking is a habit of addiction" into the statement that it is simply a habit. Because Brown & Williamson provides no evidence that other statements of its officials concerning the addictive properties of nicotine were not their own views, and the documents themselves do not support such a conclusion, FDA finds no basis to disregard those statements.

2. Brown & Williamson also challenges FDA's reliance on a report entitled, "A Tentative Hypothesis on Nicotine Addiction," arguing that it was not written by tobacco company researchers, reports no data, and is "nothing more than speculation."[881]

The report in question was sent to BATCO by the Battelle scientists who were doing contract work for BATCO on nicotine pharmacology, among other things, and contains their hypothesis of the mechanism by which smokers become addicted to nicotine. While the document hypothesizes as to the *mechanism* of addiction, it treats the existence of nicotine addiction as a fact, not hypothesis. For example, after hypothesizing that when smokers are deprived of nicotine, their endocrine systems become unbalanced, the report says: "[a] body left in this unbalanced status craves for renewed drug intake in order to restore the physiological equilibrium. This unconscious desire explains the addiction of the individual to nicotine."[882]

A copy of the report was sent by Charles Ellis to Addison Yeaman, the general counsel of Brown & Williamson. Accordingly, this document provides evidence that

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[881] *Id.* at 29.

[882] Haselbach C, Libert O, *A Tentative Hypothesis on Nicotine Addiction* (May 30, 1963), at 2. *See* AR (Vol. 20 Ref. 197-1).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

company executives had knowledge that nicotine is addictive.[883] Indeed, shortly thereafter, Yeaman wrote a memo in which he accepted the view that nicotine is addictive, and concluded, "[w]e are, then, in the business of selling nicotine, an addictive drug."[884]

3. A comment from Brown & Williamson argues that FDA has distorted its nicotine research by not recognizing that the research failed to confirm the hypotheses of its researchers. In support of this argument, Brown & Williamson offers only one example. According to the comment, the results of "Project HIPPO" failed to support its hypotheses.

The example put forward by Brown & Williamson does not establish that FDA distorted Brown & Williamson nicotine research. First, Brown & Williamson fails in its attempt to show misuse of the research project. Second, FDA relied on dozens of Brown & Williamson documents reflecting over thirty years of research, the vast majority of which Brown & Williamson does not challenge.

Project HIPPO consisted of a series of studies commissioned in the early 1960's by BATCO to investigate the role of nicotine in why people smoke, and specifically to compare the effects of nicotine with those of tranquilizers, which were perceived as marketplace competition for tobacco:

> The aim of the whole research "HIPPO" was to understand some of the activities of nicotine—those activities that could explain why

[883] Letter from Ellis C to Yeaman A (Brown & Williamson) (Jun. 28, 1963). *See* AR (Vol. 14 Ref. 165-2).

[884] Yeaman A (Brown &Williamson), *Implications of Battelle Hippo I and II and the Griffith Filter* (Jul. 17, 1963), at 4. See AR (Vol. 21 Ref. 221). Brown & Williamson protests FDA's use of this document, claiming that it was stolen from Brown & Williamson and is privileged. FDA does not believe that this document can be considered confidential, having been published in newspapers and other media throughout the United States and made available to the public without limitation by the University of California.

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> cigarette smokers are so fond of their habit. It was also our purpose to compare these effects of the new drugs called "tranquillizers" which might supersede tobacco habits in the near future.[885]

Contrary to the position taken by Brown & Williamson, Project HIPPO's authors reported that they were successful in demonstrating that nicotine was superior to tranquilizers in certain ways:

> Our investigation definitely shows that *both kinds of drugs* act quite differently, and that nicotine may be considered . . . as more "beneficial"—or less noxious—than the new tranquillizers, from some very important points of view.
>
> The so-called "*beneficial*" *effects of nicotine* are of two kinds:
>
> 1. Enhancing effect on the pituitary-adrenal response to stress;
> 2. Regulation of body weight."[886]

Although the researchers did not show that nicotine acted through certain hypothesized biochemical mechanisms, the documents demonstrate that this was not the central purpose of the research. Thus, Project HIPPO successfully demonstrated to BATCO that nicotine has two significant pharmacological effects on tobacco users: it acts like tranquilizers in helping them respond to stress, and it regulates body weight.

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4. A comment from a public health organization pointed out a number of additional statements in BATCO and Brown & Williamson internal documents acknowledging the importance of nicotine's pharmacological effects to use of tobacco products.[887] For example, the comment provided a copy of a handwritten note by S. J. Green, the long-time director of research and a board member at BATCO, in which Green

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[885] Haselbach CH, Libert O, *Final Report on Project HIPPO II* (Mar. 1963), at 1. *See* AR (Vol. 64 Ref. 321).

[886] *Id.* at 2 (emphasis added).

[887] American Society of Addiction Medicine, Comment (Dec. 29, 1995), at 3. *See* AR (Vol. 528 Ref. 97).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

says that "[t]he strong addiction to cigarette[s] removes freedom of choice from many individuals."[188] The comment also provided a copy of a 1978 BATCO document that forecast developments in technology that could be used to produce current cigarette products. The author defined "a finished smoking material" as having the following purposes: "[t]o generate smoke, taste, and pharmacological effect."[189]

FDA agrees that many of the statements to which the comment draws attention provide additional support for the determination that Brown & Williamson knows that tobacco produces pharmacological effects on consumers, including addiction, and that consumers smoke cigarettes to sustain addiction and for other pharmacological effects.

iv. Other Comments.

1. Tobacco industry comments argue that the evidence compiled by FDA of a massive industry research enterprise on nicotine pharmacology is irrelevant to the intended use of the industry's products. The comments contend that the industry conducted this research to understand and improve its products, to compare the pharmacology of new cigarettes with that of other cigarettes, to be prepared for government restrictions on tobacco products, and to respond to consumer preferences. The comments also argue that the kind of research conducted by the industry was also being done by outside researchers and reported in the public domain. Thus, according to the comments, such research need not be related to the interests of manufacturers. For these reasons,

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[188] Notes of Green SJ (1978). *See* AR (Vol. 528 Ref. 97, appendix 18).

[189] Kilburn KD (BATCO), *A Technological Forecast of the Future of Tobacco Processing* (Oct. 16, 1978), at 60. *See* AR (Vol. 258 Ref. 3524).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

according to the comments, the industry's research is not evidence of intent to affect the structure and function of the body.

FDA disagrees that the industry's extensive and sophisticated research into nicotine's pharmacological effects is irrelevant to the intended use of the products. This research establishes that the industry has actual knowledge that nicotine has powerful pharmacological effects and that consumers use tobacco to obtain those effects. "Objective intent" to affect the structure or function of the body may be established by a manufacturer's "knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it." 21 CFR 201.128 and 801.4.

The argument that other researchers conducted and published nicotine research similar to that conducted by the tobacco industry fails to provide an adequate basis to disregard the industry's research as evidence of intent. Although there may undoubtedly be other motives for this kind of research, the industry's own documents establishes that their motive is directly related to providing an adequate dose of nicotine the pharmacologically active ingredient in tobacco.

In its comments, Brown & Williamson even acknowledges that some of BATCO's most significant nicotine research was conducted, not because of outside pressure, but because Charles Ellis, senior scientific advisor to BATCO, believed that an alternative cigarette that provided only a nicotine aerosol could satisfy smokers and because he wanted to identify the "beneficial properties of nicotine."[190] Indeed, as described in the

[190] Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 23. *See* AR (Vol. 529 Ref. 104).

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Jurisdictional Analysis. Ellis believed that the research was critical "to elucidate the effects of nicotine as a beneficent alkaloid drug"[891] and because "we are in a nicotine rather than a tobacco industry."[892] *See also* Jurisdictional Analysis, 60 FR 41621–41640. Industry documents further show that the research was not merely exploratory, but was intended to be used in product development.[893]

None of the additional motives claimed by the industry for its nicotine research are inconsistent with FDA's finding that the research was conducted because the industry believes people use tobacco to obtain the pharmacological effects of nicotine, and wanted to gather information about nicotine how to ensure that tobacco products provide an adequate dose of nicotine. Each of the motives listed by the industry logically coexist with the industry's belief that consumers use tobacco for its pharmacological effects. Indeed, most of the proffered explanations themselves strongly suggest that the industry believes that the pharmacological effects of nicotine are central to the success of its products. For example, the most obvious explanation for a company's decision to compare the nicotine pharmacokinetics of a new cigarette with that of existing cigarettes is that the company believes that the pharmacological effects of nicotine are important to the success of the new product.

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[891] Ellis C (BATCO), The smoking and health problem in *Smoking and Health--Policy on Research*, Research Conference, Southampton, England (1962), at 16. *See* AR (Vol. 21 Ref. 232).

[892] Johnson RR (BATCO), Comments on Nicotine (Jun. 30, 1963), at 10-11. *See* AR (Vol. 21 Ref. 242).

[893] Dunn WL (Philip Morris Inc.), *Plans and Objectives--1979* (Dec. 6, 1978), in 141 Cong. Rec. H7668-7669 (daily ed. Jul. 25, 1995) (nicotine pharmacology research would be used to "strengthen Philip Morris R&D capability in developing new and improved smoking products"). *See* AR (Vol. 14 Ref. 175a).

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Similarly, the claim that the research on nicotine pharmacology was conducted to be prepared for government restrictions is consistent with the industry's belief that it must understand and preserve the pharmacological effects of nicotine to ensure the continued success of tobacco. This explanation for the industry's nicotine research was presented by the companies as the rationale for their nicotine analogue research. Internal documents show that the companies wanted to develop substitutes for nicotine that would mimic nicotine's pharmacological effects on the central nervous systems of smokers should restrictions prevent their continued use of nicotine.[894]

The industry's claim that it conducted research on maintaining and increasing nicotine deliveries from low-tar cigarettes because government officials "published concerns that smokers switching to lower 'tar' delivery cigarettes might change their smoking patterns if nicotine levels were too low"[895] similarly suggests that the industry believes that smokers smoke to obtain an adequate dose of nicotine. As discussed in section II.C.3.f., above, the small number of recommendations that low-tar, high-nicotine cigarettes be investigated were premised on the view that smokers use cigarettes to satisfy their dependence on nicotine and will compensate when given low nicotine cigarettes by smoking more intensely or more cigarettes to obtain an adequate dose of nicotine. It is not credible that the cigarette industry would develop cigarettes whose avowed purpose is to avoid smoker compensation, unless they share the view that smokers use cigarettes to obtain an adequate dose of nicotine.

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[894] *See, e.g.*, Kilburn KD, Underwood JG (BATCO), *Preparation and Properties of Nicotine Analogues* (Nov. 9, 1972), at 1-2. *See* AR (Vol. 31 Ref. 524-1).

[895] Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 30. *See* AR (Vol. 529 Ref. 104).

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Finally, the claim that the research was conducted to respond to consumer preferences strongly suggests that the tobacco companies understand that consumers prefer products that deliver the pharmacological effects of nicotine. Where, as here, the tobacco industry is marketing a product to which most of its consumers are addicted, satisfying consumer preferences requires the company to understand the consumer's need for nicotine in order to supply a sufficient dose of nicotine. If, on the other hand, consumer preferences were limited to taste and flavor, research on nicotine pharmacology would be irrelevant to satisfying those preferences.

Even if the record supported the industry's claim that its research was *initiated* for some purpose other than its belief that people use tobacco for nicotine's pharmacological effects (which it does not), this would not alter the fact that the research *results* demonstrated to the industry that consumers use tobacco primarily for nicotine's pharmacological effects.

2. Tobacco company comments argue that the tobacco industry's nicotine research does not establish that adults smoke solely or "nearly exclusively" to obtain nicotine. One company, while acknowledging that its parent "explored the effects of nicotine and the role it played in smoking," contends that its research "generally has concluded that the presence and effects of nicotine do not alone account for smoking enjoyment."[896]

First, the industry's contention that its research shows that nicotine does not "alone" account for tobacco use is not in any way inconsistent with FDA's conclusion that

[896] *Id.* at 22-23.

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the industry's research demonstrates that nicotine plays a central role in tobacco use. Indeed, throughout its comments, the tobacco industry implicitly acknowledges that its research demonstrates that nicotine does play a critical role in tobacco use.

Second, this research is persuasive evidence that the manufacturers intend cigarettes and smokeless tobacco products to affect the structure or function of the body of tobacco users. As described elsewhere in this notice, FDA's regulations provide that whether a product is "intended to affect the structure or any function of the body" may be established by, among other things, evidence that the vendor has knowledge that its product is being used for a pharmacological purpose, even though the product is not promoted for that purpose. 21 CFR 201.128 and 801.4. These regulations do not require the manufacturer to have knowledge that consumers use the product solely or nearly exclusively for a pharmacological purpose.

The industry's own research establishes that it has actual knowledge that consumers use tobacco products primarily for their pharmacological effects. This is persuasive and sufficient evidence that the manufacturers intend to affect the structure or function of the body. Furthermore, the tobacco industry's nicotine research, together with the other evidence in the record on consumer use, demonstrates that consumers use tobacco overwhelmingly for nicotine's pharmacological effects.

3. In the Jurisdictional Analysis, FDA reviewed the industry research and statements demonstrating that tobacco companies are aware of the high percentage of smokers who have made unsuccessful attempts to quit. This evidence demonstrates that a large proportion of tobacco users display one of the characteristic features of addiction: continued use despite attempts to quit. *See* Jurisdictional Analysis, 60 FR 41667–41673.

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One tobacco company argued that it had never determined that smokers cannot quit and that its research was not directed at control of smokers' ability to quit. Another tobacco company cited evidence that it knows many smokers would like to quit smoking, but that this is irrelevant to whether they are actually unable to quit. This company contends that the fact that many people do quit shows that tobacco is not addictive.

Both companies' comments rely on a false assumption about the relationship of the ability to quit and addiction. As described above in section II.A.3., "addiction" is not a condition that can be demonstrated only if no user is ever able to quit. Substantial percentages of users of such addictive substances as heroin and cocaine are eventually able to quit without formal treatment.[897] In fact, more than half of people seeking treatment for alcohol or drug abuse who also smoke cigarettes report that quitting smoking would be harder than giving up their other drug of abuse.[898]

The characteristic feature of all addictive substances is that it is very difficult (not impossible) to quit and that addicted users often fail despite serious attempts to do so. *See* section II.A.3., above. Tobacco company data bear this out. For example, a BATCO researcher presented data at a major BATCO conference showing that, although 40% of Canadian smokers have tried to quit, fewer than 4% were able to quit permanently within

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[897] Kleber HD, Connoy D. Don't you believe that nicotine isn't addictive, *New York Times*. Apr. 4, 1994. *See* AR (Vol. 196 Ref. 2497).

[898] Kozlowski LT, Wilkinson A, Skinner W, *et al.*, Comparing tobacco cigarette dependence with other drug dependencies, *Journal of the American Medical Association* 1989;261(6):898-901. *See* AR (Vol. 41 Ref. 92). . . .

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the past year.[899] Similarly, a Philip Morris researcher reported that of smokers who made an attempt to quit in Greenfield, Iowa, only 28% were still abstaining after 7 months.[900]

The argument that tobacco companies do not have knowledge of the low success rates experienced by tobacco users who attempt to quit defies credibility. Not only is this a matter of common knowledge, but the Council for Tobacco Research (of which every major tobacco company is or has been a member) sponsored a book on tobacco research in which the authors review, among many topics, a wealth of data on the difficulty of quitting.[901] Indeed, the very company that argued that its knowledge was limited to the fact that some smokers want to quit has argued in court that consumers should be held to the knowledge that it is very difficult to quit.[902]

4. One comment provided additional tobacco industry-funded research on nicotine pharmacology that had not been included in the Jurisdictional Analysis. FDA has confirmed that the following studies submitted with the comment are additional tobacco industry-funded studies on nicotine pharmacology and the relationship of nicotine to tobacco use:

(1) Knapp PH, Bliss CM, Wells H, "Addictive aspects in heavy cigarette smoking," *American Journal of Psychiatry* 1963;119:966-972 (supported by the Tobacco Industry Research Committee);

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[899] Proceedings of the BATCO Group R&D Smoking Behaviour-Marketing Conference, Session III (Jul. 9–12, 1984), at BW-W2-02790. *See* AR (Vol. 25 Ref. 337-1).

[900] Ryan FJ (Philip Morris Inc.), Cold Turkey in Greenfield Iowa: a follow-up study in *Smoking Behavior: Motives and Incentives*, ed. Dunn WL (Washington DC: VH Winston & Sons, 1973), at 233 (table 1). *See* AR (Vol. 8 Ref. 105).

[901] Larson PS, Silvette H, *Tobacco—Experimental and Clinical Studies: A Comprehensive Account of the World Literature* (1968), Supplement I at 300–302. *See* AR (Vol. 50 Ref. 151).

[902] Appellees brief in reply to appellants' opposition to petition for transfer, *Rogers v. R.J. Reynolds et al.*, No. 49A02-8904 CV 164 (Sup. Ct. Ind. 1990), at 7-8. *See* AR (Vol. 21 Ref. 229).

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(2) Ague C, "Nicotine content of cigarettes and the smoking habit: their relevance to subjective ratings of preferences in smokers," *Psychopharmacologia* 1972;24:326-330 (supported by the Tobacco Research Council);

(3) Beckett AH, Triggs EJ, "Enzyme induction in man caused by smoking," *Nature* 1967;216:587 (supported by the Tobacco Research Council); and

(4) Bowman ER, Turnbull LB, McKennis H, "Metabolism of Nicotine in the Human and Excretion of Pyridine Compounds by Smokers," *Journal of Pharmacology and Experimental Therapeutics* 1959; 127:92-95 (supported by the Tobacco Industry Research Committee and the American Tobacco Company).[903]

The study by Knapp, Bliss, and Wells, which was funded by the Tobacco Industry Research Committee, the predecessor to the Council for Tobacco Research, concluded that nicotine produces addiction in some tobacco users.

b. Comments on Product Research and Development To Optimize and Manipulate Nicotine Delivery

i. Comments on Specific Philip Morris Product Research and Development Projects.

1. A comment from Philip Morris argues that FDA has mischaracterized its nicotine analogue research. The comment concedes that Philip Morris conducted research in which the company developed a "behavioral, peripheral and central nervous system profile of nicotine" and compared nicotine analogues to this profile.[904] The comment asserts, however, that the company's research on nicotine analogues is not evidence of intended use because outside researchers were also investigating nicotine analogues, Philip

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[903] American Society of Addiction Medicine, Comment (Dec. 29, 1995), at appendix 9. *See* AR (Vol. 528 Ref. 97).

[904] Philip Morris Inc., Comment (Jan. 2, 1996), at 25. *See* AR (Vol. 519 Ref. 105).

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Morris provided analogues to outside researchers, and the research did not result in development of a commercial product.[905]

Philip Morris appears to be arguing that if outside researchers were also interested in nicotine analogues for unspecified reasons, then Philip Morris' own intent in conducting this research is irrelevant. FDA disagrees. Philip Morris' purpose in conducting nicotine analogue research provides evidence of the company's knowledge that nicotine's psychoactive and reinforcing effects are central to the market for tobacco. The purposes of outside researchers do not diminish or alter Philip Morris' motives in any way.

Philip Morris' internal documents and the statements of former Philip Morris employees reveal that the purpose of its nicotine analogue research was to find chemicals that mimic nicotine's effects on the central nervous system, but not its adverse effects on the cardiovascular system, that could be substituted for nicotine in cigarettes to produce a safer cigarette.[906] Specifically, Philip Morris sought to identify, through sophisticated laboratory studies in rats, whether nicotine produces discriminative stimulus effects (which predict whether a substance has mood-altering effects in humans) and reinforcing effects

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[905] Additional comments alleging that FDA misrepresented the results of Philip Morris' studies on nicotine's reinforcing properties and invalidly equated reinforcement with addiction are addressed in section II.C.6.a.i., above.

[906] *See, e.g., Regulation of Tobacco Products (Part 2): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. (Apr. 28, 1994), at 5, 35 (testimony of Victor DeNoble) *See* AR (Vol. 708 Ref. 2).

See also, Charles JL (Philip Morris Inc.), *Nicotine Receptor Program–University of Rochester* (Mar. 18, 1980) ("The original charge of the nicotine program was (1) to ascertain if the central and peripheral effects could be 'separated' and (2) to design a nicotine analogue which would have CNS activity equivalent to nicotine with little or no peripheral effect"). *See* AR (Vol. 32 Ref. 532).

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(which predict whether a substance will induce repeated compulsive use in humans), and then find analogues that could produce the same effects, for use in future cigarettes.[907]

Philip Morris' nicotine analogue research thus demonstrates that Philip Morris knows that nicotine's psychoactive and reinforcing effects are critical to the success of existing tobacco products.

2. In the Jurisdictional Analysis, FDA presented evidence that Philip Morris conducted research on acetaldehyde, another component of cigarette smoke that was hypothesized to contribute to tobacco's reinforcing effects. According to Philip Morris research reports, the objective of this research was to find the "maximally reinforcing" combination of nicotine and acetaldehyde.[908] Philip Morris argues that its research to find the maximally reinforcing combination of acetaldehyde and nicotine is not relevant to the intended use of cigarettes because the mean level of acetaldehyde in cigarettes is declining and is commonly found in proportions far from those found to be maximally reinforcing. Philip Morris also argues that its research does not establish that acetaldehyde is addictive.

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Regardless of whether Philip Morris has increased the acetaldehyde levels in its cigarettes, its research on acetaldehyde is further evidence of the company's understanding of the reinforcing properties of cigarettes and the steps it has taken to exploit those properties. In fact, there is some evidence that acetaldehyde levels in Philip Morris products have increased since 1982, the year that Philip Morris conducted its

[907] DeNoble VJ, Carron L (Philip Morris Inc.), *Progress in Behavior Pharmacology Laboratory* (Mar. 27, 1981), at 1-32. See AR (Vol. 32 Ref. 341). There is no evidence that Philip Morris tested these analogues to ensure that they produced the same "taste" as nicotine.

[908] DeNoble VJ (Philip Morris Inc.), *Project Number 1610 (Behavior Pharmacology) Objectives and Plans 1982–1983* (Jul. 20, 1982), at 2. *See* AR (Vol. 345 Ref. 5443).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

reinforcement research. According to a report in the *Wall Street Journal*, a competing tobacco company that analyzed Marlboro King Size cigarettes found that acetaldehyde levels in that brand had increased 40% between 1982 and 1991.[909]

Although a determination that acetaldehyde is a positive reinforcer is not equivalent to a finding that it is addictive, it is one of the most critical pieces of evidence that a substance is addictive. For a complete description of the role of reinforcement in addiction, see section II.A.3.c., above. Philip Morris' research into acetaldehyde's use as a multiplier of the reinforcing effects of nicotine provides evidence of Philip Morris' intent to deliver a reinforcing drug.

3. Philip Morris disputes William Farone's statement that designing cigarettes with reduced tar but an acceptable level of nicotine was a key objective of the tobacco industry. Philip Morris makes a series of arguments that purport to explain why the tar and nicotine levels in marketed cigarettes have not been reduced proportionately. The company argues that the "physics" of the filter technologies used to reduce tar and nicotine do not reduce these two constituents to the same degree, resulting in a slight increase in the nicotine-to-tar ratio, and that the Merit Ultra Lights brand of cigarettes is not an example of manipulation of nicotine-to-tar ratios.[910]

Neither of these arguments challenges Farone's statement that the tobacco industry conducted extensive product development *research* on how to reduce tar while maintaining a level of nicotine that provides the consumer with the same "pharmacological

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[909] Freedman AM, Fine tuning Marlboro, *Wall Street Journal*, (Oct. 18, 1995). *See* AR (Vol. 533 Ref. 102).

[910] Philip Morris Inc., Comment (Apr. 19, 1996), at 61-62. *See* AR (Vol. 700 Ref. 226).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

satisfaction" as full strength cigarettes.[911] Philip Morris' arguments with respect to the methods used to control nicotine-to-tar ratios are addressed in sections II.C.4., above, and section II.C.6.c.ii., below.

Tobacco industry comments also state that Farone fails to acknowledge that, beginning in the 1970's, outside scientists recommended that research be conducted on the development of a high nicotine/low tar cigarette. This argument has already been addressed above in section II.C.3.f. In this context, FDA notes that Farone is reporting on the tobacco industry's *internal* reasons for conducting the research, and these reasons are relevant to establishing the companies' intent to affect the structure or function of the body.

4. Philip Morris challenges the reliability of statements made in a declaration submitted to FDA by Ian L. Uydess, a research scientist who worked for Philip Morris from 1977 to 1981, and from 1982 to 1989. Uydess' declaration is based on his own participation in research and development projects at Philip Morris; his personal observations of activities in other parts of the company; his attendance at meetings and discussions held among the scientists, engineers and management at Philip Morris; and his close association with other scientists and senior management at Philip Morris.[912] Philip Morris argues that the information provided by Uydess is unreliable because: (1) he left Philip Morris seven years ago; (2) he did not work on the development of commercial cigarettes; and (3) his declaration reports, in part, on information relayed to him informally

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[911] Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 7. *See* AR (Vol. 638 Ref. 2).

[912] Declaration of Uydess IL (Feb. 29, 1996), at 5. *See* AR (Vol. 638 Ref. 1).

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by colleagues. In contrast, other comments argue that the reliability of Uydess' statement is shown by its consistency with the statement of other former tobacco company officials.

FDA disagrees that Uydess' declaration is unreliable or irrelevant to establishing the knowledge and actions of Philip Morris. His position and tenure at the company gave him personal knowledge of the views of Philip Morris officials on the role of nicotine in cigarettes, and of the company's research and actions in developing new products. Moreover, like Farone, Uydess' statements about the knowledge, views, and actions of Philip Morris are consistent with a large body of Philip Morris documents and statements, covering over three decades. Uydess' statements are also consistent with the recent Philip Morris document concerning Project Table, demonstrating that the company's views have not changed since Uydess left the company. The information he provided is thus corroborated by evidence already gathered by FDA.

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5. Philip Morris also challenges particular statements made by Uydess in his declaration. FDA addresses those comments that challenge statements relied on by the Agency.

Philip Morris argues that Uydess' statement that Philip Morris conducted exhaustive research on nicotine chemistry in tobacco leaf and tobacco smoke is true but irrelevant because: (1) any manufacturer in the business of selling an agricultural product develops expertise in the product; (2) tobacco chemistry is widely studied outside Philip Morris; and (3) the company's research was not used to increase artificially the nicotine yield of its commercial cigarettes.

FDA disagrees that extensive research by a tobacco manufacturer into the amount of nicotine in tobacco leaf and tobacco smoke—using highly sophisticated equipment

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developed, in part, by the company—is irrelevant to the manufacturer's intent in selling cigarettes. Philip Morris' arguments suggest that Uydess' statement relates to the company's research on tobacco chemistry in general, rather than to any specific component in tobacco. Uydess says, however, that Philip Morris' exhaustive research related specifically to nicotine and that Philip Morris "wanted to know everything there was to know about nicotine."[913] The intensity of Philip Morris' focus on nicotine provides evidence that the company knows that nicotine is central to the success of its products.

Philip Morris' public position is that if nicotine is important, it is important, like flavorants, only for its sensory appeal. The company, however, offers no evidence or argument that its exhaustive research on nicotine pharmacology is matched by its research on any other flavor or sensory aspects of nicotine. Moreover, as described in section II.C.2.a., above, Philip Morris' public position is contradicted by the views of its scientists, who have repeatedly stated that the primary reason for smoking is nicotine's pharmacological effects. FDA concludes that the extent of Philip Morris' research on nicotine is relevant to establishing its intent to affect the structure or function of the body.

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ii. Comments on Specific RJR Product Research and Development Projects.

1. RJR contends that Premier and Eclipse are not "alternative cigarettes" but conventional cigarettes, and that they were created to address public criticisms of cigarettes. RJR also disputes FDA's findings that Premier contained very little tobacco and that the nicotine in blood studies conducted on Premier show that RJR intended Premier to deliver nicotine to the smoker's blood and brain.

[913] *Id.* at 14.

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RJR's arguments concerning Premier and Eclipse are not persuasive. RJR now claims that Premier was a conventional cigarettes because it was a "roll of tobacco wrapped in paper"; "contained sugars, humectants, flavorings, tobacco paper, and a filter"; was "taxed as a cigarette"; and was "marketed for smoking taste and pleasure."[914] In fact, Premier resembled a conventional cigarette in outward appearance only. It contained a carbon tip that served as the heat source. A nicotine source had been combined with glycerol and adsorbed within alpha-alumina spheres contained within an aluminum cylinder positioned directly behind the carbon heat source. RJR informed FDA that at least 70% of the nicotine delivered by Premier was provided from spray-dried tobacco. The remaining nicotine was provided from the cut tobacco leaf surrounding this cylinder and the tobacco extract-treated paper filter positioned in front of the cellulose acetate filter.[915] Although there was a small amount of tobacco in Premier, it was not burned; the only component of Premier that was burned was the carbon heat source and some paper, to "simulate[] the ash of other cigarettes."[916]

The critical aspect of Premier is the fact that the major constituents of its smoke differed from those in the smoke of conventional cigarettes in almost every way except nicotine content.[917] In other words, virtually the only constituent of tobacco smoke that RJR designed Premier to preserve was nicotine.

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[914] R.J. Reynolds Tobacco Co., Comment (Jan. 2, 1996), 35. *See* AR (Vol. 519 Ref. 103).

[915] Letter with enclosures from Hutt PB, outside counsel for RJR, to Budich KM, FDA (Jan. 26, 1988). *See* AR (Vol. 34 Ref. 556).

[916] R.J. Reynolds Tobacco Co., *Chemical and Biological Studies on New Cigarette Prototypes That Heat Instead of Burn Tobacco* (Winston-Salem NC, 1988), at 4. *See* AR (Vol. 107 Ref. 980).

[917] *Id.* at 134-136.

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FDA does not contest that Premier was developed to address criticisms of cigarettes; undoubtedly, Premier was an attempt to make a safer cigarette. However, making a safer cigarette would not require the company to maintain a near-normal nicotine delivery, or to ensure that the nicotine was actually delivered to the smoker's blood in the same quantity as from conventional cigarettes, unless the company believed that ensuring near-normal nicotine blood levels was an essential feature of a profitable cigarette. RJR's argument that its pharmacokinetic comparisons of the nicotine levels delivered by Premier and a conventional cigarette were intended simply as comparisons of the two products, apparently without any further purpose, is unpersuasive. According to RJR's publication summarizing the studies conducted on Premier, RJR did not conduct similar pharmacokinetic studies on the delivery of any other smoke constituent to the smoker's blood.[918] This fact demonstrates that RJR believes that nicotine is the defining ingredient of cigarettes and that delivery of an adequate level of nicotine to the smoker's blood is central to the success of its products.

The RJR nicotine blood level study is also directly at odds with the company's public position that nicotine's role is limited to providing taste or flavor. The amount of nicotine delivered into a smoker's bloodstream is irrelevant to nicotine's ability to function as a flavoring agent. Nicotine absorption into the bloodstream is relevant only if the company believes that nicotine delivers pharmacological effects to the smoker and that these effects are important to the use of the product. RJR's reliance on a Surgeon General recommendation that cigarettes with low tar-to-nicotine ratios be evaluated for their

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[918] *Id.* at 457-557.

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pharmacological properties and effects on compensation[919] merely underscores RJR's understanding that the nicotine in cigarettes delivers pharmacological effects and that consumers use cigarettes for these effects.

RJR's last argument, that its study was necessary because an FDA representative later asked whether nicotine was delivered by Premier in amounts comparable to conventional cigarettes, is similarly unavailing. As RJR acknowledges in its comment, the study had already been conducted at the time FDA asked the question. Moreover, FDA asked this question because FDA saw the delivery of nicotine to the blood of smokers as relevant to whether Premier should be regulated as a drug or device.

2. RJR also argues that FDA has misused an RJR book on tobacco flavors in the Jurisdictional Analysis. FDA noted that the book, which contains over one thousand flavorants for tobacco, does not list nicotine as a flavorant.[920] RJR contends that the book describes only flavors that could be added to tobacco, and nicotine is not listed because RJR does not add nicotine.

FDA does not find RJR's argument persuasive. Even if the book were limited to flavors that "could be added" to tobacco (a limitation that is not stated in the book itself), the claim that RJR does not use it as an additive would not logically exclude it from the category of substances that "could" be added. The book does not purport to list only those substances that are actually added by RJR to its tobacco products.

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[919] Department of Health and Human Services, *The Health Consequences of Smoking: The Changing Cigarette, A Report of the Surgeon General, 1981*, at 58. *See* AR (Vol. 123 Ref. 1586).

[920] Leffingwell JC, Yound HJ (R.J. Reynolds Tobacco Co.). *Tobacco Flavoring for Smoking Products* (Winston-Salem NC: R.J. Reynolds Tobacco Co., 1972). *See* AR (Vol. 34 Ref. 591).

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Moreover, RJR's claim that it does not add nicotine raises an inconsistency. If it is the company's position that nicotine is benignly used (and controlled) in tobacco solely for its effects on flavor, and is an extremely important flavorant in tobacco, why have a policy—as RJR claims[921]—of not adding it when appropriate? The book does list many other naturally occurring components of tobacco and tobacco smoke as flavorants, apparently contemplating their addition to tobacco. That RJR policy in itself therefore seems at odds with the claim that nicotine is used for flavor.

3. RJR also maintains that FDA's reliance on an RJR patent was misplaced. In the Jurisdictional Analysis, FDA cited an RJR patent for a process that increases the nicotine content of a cigarette but masks the resulting harsh taste of the cigarette.[922] FDA used the patent to show that the tobacco industry wanted to increase nicotine in some cigarettes *despite* its harsh flavor. RJR dismisses the significance of this patent, arguing that FDA has ignored "basic principles of flavor" and that people like harsh flavors. RJR also argues that the patent is irrelevant because the process it described for increasing nicotine and masking the resulting flavor was not used in commercial cigarettes.

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RJR's argument is contradicted by its own patent and by the statements of a flavor specialist employed by the company. Both acknowledge that nicotine's harsh flavor can be unpleasant to the smoker and must be masked by the addition of sugars or other chemicals. The patent itself demonstrates that the company, as the assignee of the patent, knows that increasing nicotine past a certain point in low-tar cigarettes produces a harshness that leads to

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[921] R.J. Reynolds Tobacco Co., Comment (Jan. 2, 1996), at 50. *See* AR (Vol. 519 Ref. 103).

[922] U.S. Patent No. 4,830,028, Lawson JW, Bullings BR, Perfetti TA, R.J. Reynolds Tobacco Company, *Salts Provided from Nicotine and Organic Acid as Cigarette Additives* (May 16, 1989), at C1. *See* AR (Vol. 34 Ref. 593).

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rejection by consumers. Rather than simply keep nicotine below that point, as a company would do if nicotine were present solely for flavor, the patent describes a process for increasing nicotine and simultaneously masking its harshness. The claim that the processes in the patent were not used does not in any way undercut FDA's conclusion that the patent demonstrates RJR's knowledge that nicotine's effects on taste are sometimes negatively related to product acceptance, and RJR's desire to increase nicotine content even beyond the point where nicotine has a demonstrably negative effect on taste.

Moreover, an RJR flavor specialist has written that although nicotine is necessary for "satisfaction," its flavor in some tobacco blends is "a 'harshness' which can be choking and unpleasant," requiring that steps be taken to mask nicotine's flavor.[923]

Thus, it is clear that RJR officials recognize that nicotine's flavor is sometimes a liability that must be masked to permit nicotine to fulfill its pharmacological functions.

4. RJR comments that a document that refers to "physiological satisfaction," which FDA cited as an RJR Marketing Report, is in fact an Imperial Tobacco Co. document.[924]

FDA agrees that this document is an Imperial Tobacco Co. document rather than an RJR document. The document is one of dozens of tobacco industry documents in which the term "satisfaction" is used to describe a pharmacological effect. It is therefore relevant to establishing the industry's understanding and use of that term.

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[923] Leffingwell JC (R.J. Reynolds Tobacco Co.), Nitrogen components of leaf and their relationship to smoking quality and aroma, presented at the 30th Tobacco Chemists' Research Conference, at 9. *See* AR (Vol. 28 Ref. 450).

[924] Imperial Tobacco Ltd., *Matinee Marketing Strategy* (1971) ("A cigarette that delivers physiological satisfaction, yet is low in tar and nicotine, must surely be a major objective"), quoted in Memorandum to File from Joyal C (Dec. 27, 1992), at 11. *See* AR (Vol. 27 Ref. 384).

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iii. Comments on Specific Brown & Williamson Product Research and Development Projects.

1. A comment from Brown & Williamson argues that FDA has distorted its nicotine research by not recognizing that the research was not commercialized. According to the comment, Project ARIEL was never commercialized.

ARIEL was an alternative cigarette, developed by Charles Ellis, and referred to by BATCO researchers as a "device[] for the controlled administration of nicotine."[925] ARIEL eliminated almost every ingredient of conventional cigarettes other than nicotine. Its purpose was to provide "the same benefits, pleasure and satisfaction without the disadvantages" of a conventional cigarette.[926] The relevance of this product to intent is that it demonstrates that BATCO regarded nicotine as the essential ingredient in, and the source of the pleasure and satisfaction from, cigarettes. ARIEL's development demonstrates Brown & Williamson's knowledge of and belief in nicotine's central role in cigarettes, regardless of its ultimate failure to be accepted by consumers, or Brown & Williamson's decision not to market it.

2. As described above, a BATCO study entitled "Project Wheat" was conducted to determine the level of nicotine preferred by smokers and correlate it with the extent to which the smoker relies on cigarettes to meet "inner needs."[927] A smoker's inner need level was defined by the extent to which the smoker used nicotine to relieve stress,

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[925] Minutes of BATCO Research Conference at Hilton Head Island, SC (Sep. 24–30, 1968), at 3. *See* AR (Vol. 31 Ref. 525).

[926] U.S. Patent No. 3,258,015, Ellis CD, Dean C, Schachtner H, *et al.*, Battelle Memorial Institute, *Smoking Device* (Jun. 28, 1966). *See* AR (Vol. 34 Ref. 569).

[927] Wood DJ, Wilkes EB (BATCO), *Project Wheat - Part I: Cluster Profiles of U.K. Male Smokers and their General Smoking Habits* (Jul. 10, 1975), at 1. *See* AR (Vol. 20 Ref. 204-1).

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aid concentration, avoid weight gain, or reduce craving. BATCO hypothesized that "the inner need dimension was probably defining a requirement for nicotine."[928] FDA pointed out that inner need therefore correlated with the extent to which a smoker used cigarettes for pharmacological effects. Project Wheat was intended to allow BATCO to market cigarettes with different nicotine levels designed to satisfy identified groups of consumers. Brown & Williamson argues that FDA had no basis for concluding that a smoker's inner need was defined by the extent to which the smoker used cigarettes for the drug effects of nicotine, that Project Wheat failed to find any significant correlation between inner need levels and preferred nicotine delivery, that the term "inner need" came from an outside researcher, not BATCO, and that FDA falsely suggested that Project Wheat identified an allegedly "addictive" dose of nicotine.

Brown & Williamson's attempts to discredit FDA's characterization of Project Wheat are not persuasive. FDA relied on the study as evidence that Brown & Williamson had conducted research on the dose of nicotine required by consumers with the purpose of designing cigarettes to satisfy their nicotine requirements. Brown & Williamson acknowledges that Project Wheat was designed to determine whether smokers who smoked to satisfy an "Inner Need" had preferred nicotine delivery levels, and that this information was to be used to design cigarettes to meet their needs.[929] These facts alone demonstrate that it was the tobacco company's intention to produce cigarettes with satisfying doses of nicotine. (Nowhere did FDA state that the study was intended to establish "addictive" doses of nicotine.)

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[928] *Id.* at 5.

[929] Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 43-44. *See* AR (Vol. 529 Ref. 104).

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Moreover, both Project Wheat and other Brown & Williamson research demonstrate that the company knew that "Inner Need" level corresponded to the smoker's use of cigarettes for pharmacological effects. Project Wheat researchers concluded that future studies to design cigarettes with acceptable nicotine levels should classify smokers along a single dimension of inner need that might correspond to "pharmacological addiction":

> [I]t would be preferable to position respondents along the single dimension of Inner Need. . . . the suggestion is very much in line with that made by Russell . . . who . . . concluded that *it might prove more useful to classify smokers according to their position on a single dimension of pharmacological addiction* rather than in terms of their profiles on the six types of smoking.[930]

Brown & Williamson's assertion that stress relief, aided concentration, and weight control are not among the principal pharmacological effects of nicotine is not credible. In fact, as early as 1962, Project HIPPO concluded that nicotine's most significant pharmacological benefits were its ability to relieve stress and to control weight gain.[931]

Contrary to Brown & Williamson's argument, Project Wheat found a correlation between inner need level and preferred nicotine delivery.[932] Thus, the Project Wheat researchers concluded that inner need correlated with preferred nicotine delivery and agreed with Russell that inner need is related to pharmacological addiction.

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[930] Wood DJ (BATCO), *Project Wheat - Part 2: U.K. Male Smokers: Their Reactions to Cigarettes of Different Nicotine Delivery as Influenced by Inner Need* (Jan. 30, 1976), at 49 (citation omitted) (emphasis added). *See* AR (Vol. 20 Ref. 204-2).

[931] Haselbach CH, Libert O, *Final Report on Project HIPPO II* (Mar. 1963), at 2. *See* AR (Vol. 14 Ref. 163-1).

[932] Wood DJ (BATCO), *Project Wheat - Part 2: U.K. Male Smokers: Their Reactions to Cigarettes of Different Nicotine Delivery as Influenced by Inner Need* (Jan. 30, 1976), at 47-48 ("High Need clusters tend to prefer relatively high nicotine cigarettes, and . . . their optimum nicotine delivery is certainly higher than is that of the Low Need clusters.") *See* AR (Vol. 20 Ref. 204-2).

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3. A comment from Brown & Williamson claims that the company has never marketed a product that used "elasticity" to enable smokers to compensate for lowered nicotine yields. The company concedes that internal documents show that "BATCO explored the possibility of using its knowledge of compensation in the development of low 'tar' products" but claims that these were only theoretical discussions.[933]

FDA relied, in part, on the industry's product development research on increasing nicotine as evidence that the industry understands that tobacco satisfaction is a function of the pharmacological effects of nicotine and of the industry's attempts, successful or not, to ensure that tobacco users receive sufficient nicotine to achieve those effects. FDA did not rely on this research as evidence that the researched products were marketed.

In fact, however, there is good reason to believe that Brown & Williamson, as well as other tobacco companies, have incorporated "elasticity" into their marketed products. For example, Brown & Williamson's Barclay cigarettes were promoted as ultra-low cigarettes, with advertised deliveries of 1 mg tar and .02 mg nicotine, as measured by the FTC method. *Federal Trade Commission v. Brown & Williamson*, 778 F.2d 35, 37 (D.C. Cir. 1985). Philip Morris and RJR complained to the FTC that Barclay's channel-ventilated filter system allowed the cigarette to produce low tar and nicotine yields when measured by the FTC (smoking machine) method, but to actually deliver far more tar and nicotine to the smoker. According to the complaint, the FTC smoking machine is able to "smoke" the cigarette without obstructing Barclay's unique ventilation system, but "when the cigarette is smoked between human lips its air ventilation system is inevitably

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[933] Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 42. *See* AR (Vol. 529 Ref. 104).

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obstructed and the cigarette delivers disproportionately more tar and nicotine than other comparably rated cigarettes." *Id.* at 37.

The FTC brought an enforcement proceeding to enjoin Brown & Williamson from using the FTC tar and nicotine figures in Barclay advertisements. *Federal Trade Commission v. Brown & Williamson*, 580 F. Supp. 981 (D.D.C. 1983), *aff'd in part, rev'd in part*, 778 F.2d 35 (D.C. Cir. 1985). The district court found, and the Court of Appeals agreed, that use of the FTC tar and nicotine figures for Barclay was false and misleading, because—primarily as a result of its channel-ventilated filter system—Barclay delivers significantly more tar and nicotine to the smoker than indicated by the FTC yields. 580 F. Supp. at 989; 778 F.2d at 41-42. Thus, Barclay represents a clear example of the use of filter technology to provide elasticity, i.e., to enable the smoker to extract more nicotine from the smoke than the advertised yield.

Brown & Williamson argues that Barclay is not an example of a product designed to provide elasticity, and that there is no evidence to support FDA's claim that the channel-ventilated filter boosts nicotine delivery. FDA disagrees. The district court opinion in *Federal Trade Commission v. Brown & Williamson* demonstrates that Barclay cigarettes deliver substantially more nicotine than their advertised yields and that this increase in nicotine delivery over the machine-tested yield is due to compromising the channel-ventilated filter during human smoking. The district court cited a study submitted by Brown & Williamson, which found that "smokers who smoked Barclay received approximately 1-1/2 to 2 times as much nicotine into their systems as smokers of the other cigarettes [with comparable FTC ratings] tested." 580 F. Supp. at 988. The court also

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found that the increase in nicotine and tar deliveries was due to compromising the ventilation system under actual smoking conditions. 580 F. Supp. at 989.

The conclusion that Barclay was designed to provide elasticity is also supported by evidence that Barclay was reported to contain significantly more nicotine than comparable cigarettes. As described above in section II.C.4., an independent study conducted in 1982 showed that Barclay had both the highest nicotine concentration and the most total nicotine in the rod of all the cigarette brands tested, including regular strength (high tar/high nicotine) cigarettes.[934] Compared to the other cigarettes with comparable FTC nicotine ratings (≤0.2 mg nicotine, as published in 1981 FTC Report) that were tested, Barclay contained a tobacco blend with a 50% to 95% higher nicotine concentration, and 20% to 85% more total nicotine. Thus, while Barclay had among the lowest FTC yields, it delivered a significantly higher level of nicotine during human smoking because (1) it contained more nicotine than any comparable cigarette, and (2) the nature of the filter permitted smokers to defeat the ventilation system and obtain substantially more nicotine than the advertised yield (1-1/2 to 2 times the nicotine of comparable cigarettes, according to Brown & Williamson's own study).

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iv. Other Comments.

1. Comments from the tobacco industry argue that the tobacco company studies cited by FDA do not support the finding that smokers compensate. One comment argues that Brown & Williamson and BATCO researchers did not acknowledge that

[934] *Regulation of Tobacco Products (Part 3): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 173 (Jun. 23, 1994) (data from Neal Benowitz). *See* AR (Vol. 709 Ref. 3).

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smokers compensate to obtain a dose of nicotine that satisfies a physiological need. This comment does concede, however, that it is "hardly news" that "the phenomenon of compensation was internally 'recognized' or 'acknowledged' by tobacco manufacturers."[935] This comment also argues that reductions in tar and nicotine yields have resulted in reductions of the amount of nicotine obtained by smokers. On the other hand, a comment from a public health organization provided additional examples of industry statements and research on compensation.[936]

FDA has reviewed the studies relied on in this section of the Jurisdictional Analysis and concludes that they provide a wealth of evidence that the tobacco industry understands that smokers compensate to obtain a desired dose of nicotine. The contention that these studies fail to demonstrate compensation cannot be supported. For example, BATCO researchers stated in 1984 that "it is accepted that nicotine is both the driving force and the signal (as impact) for compensation in human smoking behavior."[937]

A large number of additional industry studies cited by FDA found that compensation occurred to one degree or another. *See* Jurisdictional Analysis, 60 FR 41659–41666. Throughout these studies and conference reports, tobacco company officials consistently recognize that compensation behaviors occur to adjust nicotine dose. The public health organization comment provided several additional examples of tobacco industry acknowledgment that compensation occurs because smokers are attempting to

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[935] Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 40. *See* AR (Vol. 529 Ref. 104).

[936] American Society of Addiction Medicine, Comment (Dec. 29, 1995), Table 6. *See* AR (Vol. 528 Ref. 97).

[937] Minutes of BATCO Group R&D Smoking Behaviour-Marketing Conference, Session III (Jul. 9-12, 1984), at 56. *See* AR (Vol. 25 Ref. 325-1).

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maintain their customary nicotine dose. For example, a 1981 monograph on nicotine published by the Tobacco Advisory Council (an industry organization of which BATCO was a member) reviewed the evidence on compensation and concluded that while regulation of nicotine intake is not consistently seen in every study:

> Human subjects appear to modify their smoking behaviour to maintain the total dosage of nicotine when they smoke cigarettes of varying nicotine content. . . . Studies of nicotine antagonists indicate that smokers seek an effective brain level of nicotine when modifying their smoking behaviour.[938]

Accordingly, the industry's research amply supports FDA's conclusion that the tobacco industry knows that smokers use cigarettes to "compensate"—to obtain desired doses of nicotine.

2. One comment from a tobacco manufacturer argues that "much" of the nicotine-related research did not result in alterations to marketed products, and a comment from another cigarette manufacturer argues that its product development research did not result in the addition of "extraneous nicotine."

The claim that some of the industry's research did not result in changes to commercial-marketed products does not alter the relevance of the industry's research to establishing manufacturers' awareness of the pharmacological effects of nicotine. As noted above, the knowledge produced by the research is evidence of intended use. Moreover, there is a great deal of evidence that the knowledge was acted upon. Even the industry comments do not claim that none of the research was acted upon. For example, the brands of cigarettes advertised as lowest in tar and nicotine have the highest

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[938] Cohen AJ, Roe JC (Tobacco Advisory Council), *Monograph on the 'Pharmacology and Toxicology of Nicotine'* (1981), at 38 (citation omitted). *See* AR (Vol. 34 Ref. 583).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

concentrations of nicotine on the market, reflecting industry to ensure that nicotine levels in low-yield products do not fall below minimum levels that consumers will accept. *See* section II.C.4.a., above.

Finally, the argument that none of the product development research resulted in the addition of "extraneous nicotine" to commercial cigarettes is irrelevant to establishing intended use. Whether or not this statement is true, the research, in and of itself, establishes the knowledge of tobacco manufacturers that nicotine delivery is essential to the success of their products. In addition, the evidence shows that nicotine has actually been manipulated in commercial cigarettes, demonstrating that tobacco manufacturers have not merely researched but have taken affirmative steps to ensure the delivery of an adequate dose of nicotine. *See* Jurisdictional Analysis, 60 FR 41693–41733. It is the fact that the industry has manipulated nicotine delivery, rather than the manner in which it is accomplished, that is relevant to establishing the intended use of these products.

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c. Comments on Nicotine Manipulation and Control

i. Comments on the Use of High-Nicotine Blends in Low-Yield Cigarettes.

1. The cigarette manufacturers contend that the use of high-nicotine blends in low-tar cigarettes does not affect the nicotine delivery of these cigarettes. According to the manufacturers, the increase in nicotine from the use of high-yield blends is more than offset by other design features, such as a reduction in the total mass of tobacco in the cigarette and increased filtration and ventilation.

The Agency disagrees. It is beyond reasonable dispute that the use of high-nicotine blends does affect nicotine deliveries. Indeed, the joint comment of the manufacturers acknowledge this point. The comment concedes that "nicotine content of

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the leaf" is one of the "*factors that determine the nicotine yield in the cigarette smoke.*"[939] Of the four factors that the comment lists as determining nicotine yield, two of the factors —"the blend itself" and "the percentage of processed tobaccos"[940]—relate directly to the concentration of nicotine in the cigarette rod. Similarly, Alexander Spears, the vice chairman and chief operating officer of Lorillard, has acknowledged that among other factors, "*the nicotine yield of a cigarette is determined by the nicotine content of the tobacco.*"[941]

Although it may be true that other design features of low-tar cigarettes reduce nicotine deliveries, the use of high-nicotine blends is designed to *offset* those reductions. Thus, high-nicotine blends result in higher nicotine deliveries than would be provided by a low-tar cigarette that did not use such blends.

Moreover, the nicotine yields measured on an FTC smoking machine do not accurately predict the amount of nicotine that will be inhaled and absorbed by smokers because smokers of low-yield products frequently compensate for the low nicotine deliveries by inhaling more deeply or puffing more frequently. *See* Jurisdictional Analysis, 60 FR 41573–41574. The use of higher nicotine blends in low-yield cigarettes increases the total amount of nicotine that is available to be extracted by smokers.

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[939] Joint Comment of Cigarette Manufacturers, Comment, (Jan. 2, 1996), Vol. IV, at 69 (emphasis added). *See* AR (Vol. 535 Ref. 96).

[940] *Id.* at 79.

[941] Spears AW (Lorillard Tobacco Co.), *Factors Affecting Smoke Delivery of Nicotine and Carbon Monoxide*, presented at the 1975 Symposium-Nicotine and Carbon Dioxide (Nov. 17-18, 1975), in *Symposium Proceedings-1*, 12-18, at 13 (emphasis added). *See* AR (Vol. 27 Ref. 395a).

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2. Brown & Williamson's comments concede that it used Y-1, a high-nicotine tobacco, in marketed cigarettes. The comments assert, however, that Y-1 "was never used by B&W for the purpose of altering the ratio of nicotine to tar in the smoke of any commercialized brands."[942] What is beyond dispute, however, is the original purpose of the creation of Y-1. As described in section II.C.3.c.iii., Brown & Williamson developed Y-1 as a "blending tool" so that it could maintain nicotine levels while tar levels dropped. Y-1 is thus a central example of product research and development to enhance nicotine deliveries.

ii. Comments on Nicotine Deliveries and Nicotine-to-Tar Ratios.

1. The cigarette industry asserts in its comments that the reduction in the nicotine delivery of cigarettes over the last 40 years demonstrates that the industry has not sought to control or manipulate nicotine. According to the industry, nicotine deliveries have dropped by 60% over the last 40 years. The industry maintains that the fact that cigarette manufacturers have reduced nicotine deliveries shows that the manufacturers do not control or manipulate nicotine deliveries to provide a pharmacologically active dose of nicotine.

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The Agency agrees that nicotine deliveries as measured by smoking machines have declined over the last 40 years. This comparison is misleading, however. The recent trends show that nicotine deliveries have stopped declining and are, in fact, *increasing* — especially in low-tar cigarettes. From 1982 to 1991, the nicotine deliveries in the lowest-tar category of cigarettes increased approximately 15%. *See* Jurisdictional Analysis, 60

[942] Brown & Williamson Tobacco Corp., Comment (Jan. 2, 1996), at 32. *See* AR (Vol. 529 Ref. 104).

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FR 41731. Although the industry maintains that "[n]icotine levels follow the tar level" in "essentially perfect correlation"[943] and that this correlation shows that the industry does not manipulate nicotine,[944] nicotine deliveries did not follow tar deliveries during this period. Rather, while nicotine deliveries were increasing from 1982 to 1991, tar deliveries declined or remained essentially flat.[945]

The recent trend of increasing nicotine deliveries in low-tar cigarettes supports the Agency's finding that the cigarette manufacturers have controlled and manipulated nicotine to maintain a pharmacologically active dose. The trend is evidence that as tar deliveries dropped to low and ultra-low levels in the late 1970's and the 1980's, the manufacturers took steps to maintain a pharmacologically active nicotine dose by enhancing nicotine deliveries.

The overall trend in nicotine deliveries is also fully consistent with—and indeed corroborates—the Agency's position. Forty years ago, cigarettes delivered over 2.5 mg of nicotine per cigarette.[946] According to tobacco industry documents, however, nicotine deliveries as low as 0.5 to 0.8 mg per cigarette "provide sufficient nicotine to the blood to produce the stimulation and relaxation effects desired by the smoker."[947] Thus, nicotine

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[943] *Regulation of Tobacco Products (Part 1). Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 378 (Mar. 25, 1994) (statement of Alexander Spears). *See* AR (Vol. 707 Ref. 1).

[944] *Id.*

[945] From 1982 to 1991, nicotine deliveries increased in ultra-low-tar, low-tar, and high-tar cigarettes. Tar deliveries, however, decreased in the high-tar and low-tar categories and increased only marginally (approximately 3%) in the ultra-low-tar category. *See* Jurisdictional Analysis, 60 FR 41728-41731.

[946] Joint Comment of the Cigarette Manufacturers, Comment (Jan. 2, 1996), Vol. III. "Sales Weighted Average 'Tar' and Smoke Nicotine" Graph. *See* AR (Vol. 535 Ref. 96).

[947] Seneus M (R. J. Reynolds Tobacco Co.), *Some Effects of Smoking* (1976/1977), at 12 (emphasis added). *See* AR (Vol. 700 Ref. 593).

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deliveries could be reduced significantly from 1956 levels without interfering with the ability of cigarettes to satisfy smokers' addiction and to provide other desired pharmacological effects of nicotine.

Once nicotine deliveries neared the minimum thresholds identified by the cigarette manufacturers, however, the manufacturers reversed course and began to enhance nicotine deliveries. As the tobacco industry documents in the record indicate, the industry feared that at these low levels, cigarettes might not deliver sufficient nicotine to smokers. *See* section II.C.3., above. Consequently, the cigarette manufacturers began to take measures to raise nicotine deliveries, such as using nicotine-rich tobacco blends in ultra-low tar cigarettes. *See* section II.C.4., above. The trend of increasing nicotine deliveries since 1982 reflects these actions.

Moreover, the Agency disagrees with the manufacturers that efforts to enhance nicotine deliveries will necessarily be reflected in the nicotine deliveries measured by smoking machines. To the contrary, the evidence in the record indicates that some of the methods used by the cigarette manufacturers to enhance nicotine deliveries are *not* reflected in the measured nicotine deliveries. The use of "elasticity" technologies, such as ventilation systems that can be blocked by smokers, is one example. As described in section II.C.4.b, these technologies are designed to allow smokers to inhale more nicotine than would be measured by a smoking machine. Similarly, the use of ammonia technologies to liberate "free" nicotine, which is described in section II.C.4.c., has effects

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BATCO and Philip Morris researchers reached similar conclusions. According to one BATCO research study, a smoker's "nicotine requirement" is "about 0.8 mg per cigarette." Notes on the BATCO Group R&D Conference at Duck Key, FL (Jan. 12-18, 1974), at 2. *See* AR (Vol. 25 Ref. 327). Likewise, Philip Morris researchers recognized that "[t]he physiological response to nicotine can readily be elicited by cigarettes delivering in the range of 1 mg of nicotine." Dunn WL (Philip Morris Inc.), *Motives and Incentives in Cigarette Smoking* (1972), at 4. *See* AR (Vol. 12 Ref. 133).

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on nicotine absorption that are not reflected in the nicotine levels measured by a smoking machine.

2. The cigarette industry criticizes various aspects of FDA's methodology in calculating nicotine deliveries. The industry's comments assert that these alleged methodological problems make FDA's findings of increased nicotine deliveries unreliable.

The Agency disagrees with these comments. The industry itself acknowledges in its comments that nicotine deliveries have increased among the lowest-tar cigarettes.[948] This acknowledgment renders most of the industry's specific methodological objections irrelevant because it confirms the Agency's finding that nicotine deliveries have increased in the ultra-low-delivery category.

Moreover, the specific methodological comments of the cigarette industry are not well founded, as discussed below.

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First, the cigarette industry is mistaken when it argues that FDA chose to use 1982 as its reference year to distort the trends in nicotine deliveries. FDA did not calculate these deliveries. Rather, these figures were calculated by the Federal Trade Commission (FTC), which annually reports tar and nicotine data for cigarettes. The FTC began its analysis in 1982 because this was the first year in which computer-readable data was available in the FTC files.

Second, the cigarette industry is mistaken when it suggests that the FTC did not follow the approach recommended by the Surgeon General for calculating sales-weighted tar and nicotine deliveries. In fact, the FTC followed this approach.

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[948] Joint Comment of Cigarette Manufacturers, Comment (Jan. 2, 1996), Vol. III, at 206. *See* AR (Vol. 535 Ref. 96).

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Third, FDA disagrees that brand shifting accounts for the increase in nicotine deliveries observed in the data. Brand shifting is unlikely to significantly affect reported average deliveries because brand shifts can occur in both directions (and so tend to cancel each other out) and because no single variety of cigarettes has a sufficient proportion of the sales to affect category averages.

Moreover, the data are inconsistent with the industry's brand-shifting theory. The data show that tar deliveries have either declined slightly (high- and low-tar categories) or increased slightly (ultra-low-tar category), while nicotine deliveries have increased significantly in these categories. If brand shifting was in fact causing the rise in nicotine deliveries in the three categories, tar deliveries should have risen similarly, which they did not. Most significantly, brand shifting cannot explain the increase in nicotine deliveries that was observed when all brands (from all three categories) were averaged together.

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Fourth, FDA disagrees that normal analytical variation explains the observed increases in nicotine deliveries. The statistical chance that analytical variation could explain the results is vanishingly small. To begin with, the laboratory equipment used to measure nicotine and tar yields produces generally consistent results. The equipment has 20 ports, four of which are dedicated to measuring the tar and nicotine content of "monitor cigarettes" to guard against any "drifting" of the equipment.

Moreover, the trends reported by FDA from the FTC data reflect the results of literally tens of thousands of individual measurements of cigarettes. The reported tar and nicotine yield for any specific cigarette variety in a given year is the average of the test results of 100 individual cigarettes. The average tar and nicotine yields for all cigarette varieties in a given yield category, such as low-yield cigarettes, is the average of the

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reported tar and nicotine yields for each cigarette variety in the category. Any analytical variation in the testing of individual cigarettes will have at most a very small effect on the averages reported from so large a sample size.

Fifth, the questions raised by the industry regarding the origin of the sales-weighted data are groundless. The data for 1984, 1985, and 1986 came from the FTC. Although the FTC may not have issued a report on tar and nicotine deliveries for each of those years, the FTC informed the Agency that it did nonetheless collect tar and nicotine data for these years. The 1991 and 1992 data do use information from slightly fewer brands than the brands listed in the FTC's published reports for those years; however, the explanation is that the FTC did not have tar, nicotine, and sales data for every single brand listed in the published reports. Only those brands for which data were missing were eliminated by the FTC in calculating the sales-weighted averages. The sales data used by the FTC to calculate the sales-weighted averages came from the tobacco manufacturers.

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Finally, contrary to the industry's assertion, FDA did put the data and analysis it relied upon in the administrative record.[949]

Thus, contrary to the comments of the industry, FDA finds that a reasonable methodology was used to calculate nicotine deliveries.

3. Philip Morris asserts that it has few cigarettes with an enhanced nicotine/tar ratio of 0.10, compared to the naturally occurring ratio of 0.07. The company argues that this is evidence that it does not design its cigarettes to enhance nicotine deliveries. Philip Morris further asserts that two Philip Morris brands with nicotine/tar ratios of

[949] *See* Letter from Schultz WB (FDA), to Merrill R (Covington & Burling) (Dec. 27, 1995). *See* AR (Vol. 711 Ref. 7).

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approximately 0.10 analyzed by Rep. Henry A. Waxman and cited by FDA (Merit Ultima and regular Benson & Hedges filtered cigarettes) do not reflect intentional nicotine manipulation.

The Agency disagrees that cigarettes with an elevated nicotine/tar ratio of 0.10 are uncommon. In 1995, for instance, over 90 varieties of cigarettes had a nicotine/tar ratio of 0.10 or higher.[950] Particularly among ultra-low-tar cigarettes, there are many examples of cigarettes with relatively enhanced nicotine deliveries and nicotine/tar ratios. Over 40% of cigarettes with tar deliveries of 5 mg or less have an enhanced nicotine/tar ratio of 0.10 or greater.[951] One example is the Merit Ultima, which is manufactured by Philip Morris and has a nicotine/tar ratio of 0.10.[952] Other examples are RJR's Winston Ultra Lights 100's and king-size Camel Ultra Lights, which have tar deliveries of 0.5 mg and nicotine deliveries of 0.5 mg, resulting in a nicotine/tar ratio of 0.10.[953] The deliveries of nicotine and tar in the Winston Ultra Lights 100's and the king-size Camel Ultra Lights are exactly the deliveries that RJR researchers recommended to produce "a low tar value" while "maintaining the nicotine as high as possible."[954] The existence of low-tar cigarettes with relatively elevated nicotine deliveries is compelling evidence that cigarette manufacturers design these cigarettes to provide enhanced nicotine deliveries.

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[950] Federal Trade Commission, *Report of "Tar," Nicotine, and Carbon Monoxide of the Smoke of 1107 Varieties of Domestic Cigarettes* (1995). *See* AR (Vol. 535 Ref. 96, vol. IV.B).

[951] *Id.*

[952] *Id.*

[953] *Id.*

[954] Senkus M (R.J. Reynolds Tobacco Co.), *Some Effects of Smoking* (1976/1977), at 10. *See* AR (Vol. 700 Ref. 593).

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Moreover, even if no ultra-low-tar cigarettes had a nicotine/tar ratio of precisely 0.10, this would prove very little. As discussed in section II.C.3.a., Philip Morris' product development efforts concluded that "the optimum nicotine to tar . . . ratio for a [low-delivery] cigarette is *somewhat higher* than that occurring in smoke from the natural state of tobacco."[955] This research did not conclude that the "somewhat higher" ratio had to be a ratio of 0.10 (which is more than 40% higher than the "natural ratio" of 0.07) or greater. Consistent with Philip Morris' product development recommendations, most of the lowest-yield cigarettes do in fact have "somewhat higher" nicotine/tar ratios of 0.08 or greater. *See* Jurisdictional Analysis, 60 FR 41724.

The Agency rejects Philip Morris' claim that the enhanced nicotine/tar ratio of 0.10 in Merit Ultima can be explained by "the physics of low-yield filtration and ventilation."[956] FDA's own analysis has shown that the Merit Ultima uses a blend richer in nicotine than the blends used in either the Merit Filter 100's or the Merit Ultra Lights. See Jurisdictional Analysis, 60 FR 41723–41724. This deliberately chosen nicotine-rich blend contributes to the elevated nicotine/tar ratio in the Merit Ultima—apart from any effects of filtration or ventilation. *See* section II.C.4.a.ii. Moreover, to the extent that filtration and ventilation contribute to the elevated nicotine/tar ratio, this effect is the result of deliberate design decisions. *See* section II.C.4.b.

The Agency is also not persuaded that the enhanced nicotine/tar ratios in the regular Benson & Hedges filtered cigarettes can be dismissed as "minuscule variations" in

[955] Jones B, Houck W, Martin P (Philip Morris Inc.), *Low Delivery Cigarettes and Increased Nicotine/Tar Ratios, A Replication* (Oct. 1975), in 141 Cong. Rec. H8132 (daily ed. Aug. 1, 1995) (emphasis added). *See* AR (Vol. 711 Ref. 6).

[956] Philip Morris Inc., Comment (Jan. 2, 1996), at 43. *See* AR (Vol. 519 Ref. 105).

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tar and nicotine deliveries. A statistical analysis of the cigarettes prepared for and released by Rep. Waxman concluded that the possibility that the cigarette's enhanced nicotine/tar ratio could be explained by random fluctuations in tar and nicotine levels was virtually zero.[957]

iii. Comments on Chemical Manipulation.

1. Comments from the tobacco industry acknowledge that cigarette manufacturers add ammonia compounds to tobacco. However, the comments argue that the addition of ammonia does not have pharmacological significance because virtually all nicotine in cigarette smoke is absorbed into the bloodstream regardless of the pH of the smoke; because substantial amounts of ammonia would be required to raise smoke pH from 6.0 to 7.5 or 8.0; and because ammonia compounds do not increase the efficiency of the transfer of nicotine from the tobacco to the smoke.

The Agency disagrees with these comments. They conflict with the evidence from the cigarette industry documents in the record, as well as with basic scientific principles.

The evidence in the record demonstrates that the cigarette manufacturers add ammonia compounds to cigarettes to produce several pharmacological effects. As described in the industry documents, the pharmacologically significant effects of adding ammonia compounds to tobacco are (1) to increase the transfer of nicotine from the cigarette to the smoke; (2) to increase the rate of nicotine absorption in the mouth; and (3) possibly to increase the speed of nicotine absorption in the lungs. *See* section II.C.4.c.

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[957] Statement of Waxman HA. 141 Cong. Rec. H8009 (daily ed. Jul. 31, 1995). *See* AR (Vol. 27 Ref. 376a).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

Each of these three effects of adding ammonia compounds is significant even if the industry were correct that the lungs absorb virtually all of the nicotine that is inhaled.[958] The first effect—increasing the transfer of nicotine from the cigarette to the smoke—is significant because it increases the quantity of nicotine *delivered* to the lungs. Most of the nicotine in a cigarette never enters the mouth of a smoker. Rather, it is trapped in the filter; lost to the atmosphere; or destroyed or decomposed by the heat of the cigarette.[959] According to the statement of Dr. Farone, the former Philip Morris Director of Applied Research, however, the effect of adding ammonia compounds is "to deliver more of the available nicotine in the blend to the smoker."[960] Documents from the American Tobacco Company make a similar point, asserting that the use of alkaline compounds will "increas[e] the amount of nicotine that is transferred from the tobacco to the mainstream smoke."[961]

The second effect is likewise significant regardless of the efficiency of nicotine absorption in the lungs. This effect is to increase the amount of nicotine that the smoker

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[958] In fact, it is not clear that the lungs absorb virtually all the nicotine that is inhaled. According to one researcher, "[d]epending on inhalation patterns, retention times, and related factors, smokers may retain anywhere from 30% or less up to 90% or more of the total nicotine generated and delivered via the inhaled smoke." Huber GL, Physical, chemical, and biological properties of tobacco, cigarette smoke, and other tobacco products, *Seminars in Respiratory Medicine* 1989;10:297-332, at 304. *See* AR (Vol. 333 Ref. 5045).

[959] Armitage AK, Dollery CT, George CF, *et al.*, Absorption and metabolism of nicotine from cigarettes, *British Medical Journal*, 1975:313-316, at 315 ("[N]o more than 25% of the total nicotine content of the cigarette is likely to appear in the mainstream smoke. Most of the nicotine is lost into the surrounding air and sidestream smoke or is retained in the butt"). *See* AR (Vol. 131 Ref. 1462).

[960] Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 13. *See* AR (Vol. 638 Ref. 2).

[961] Bodenhamer NL (American Tobacco), Leaf Services Monthly Report for June (Jun. 30, 1980). *See* AR (Vol. 27 Ref. 385).

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absorbs through the *mouth*—not the lungs. Adding ammonia compounds raises the pH of the tobacco smoke. *See* section II.C.4.c. According to RJR researchers, by raising pH in a low-tar cigarette from just 6.0 to 6.5, "*you increase the nicotine transfer in the mouth.*"[962]

The third effect is a possible increase in the speed of nicotine absorption in the lungs. The increase in pH caused by the addition of ammonia compounds increases the proportion of "free" or "extractable" nicotine in the smoke. *See* section II.C.4.c. According to documents from BATCO, Brown & Williamson's parent company hypothesized that "with a higher 'extractable' nicotine, nicotine reaches the brain more quickly."[963] The BATCO researchers further postulate that "in human smoking a difference in the time of nicotine absorption of tenths of a second may be important."[964]

In light of this evidence from former cigarette industry employees and the industry's own documents, the industry's assertion that adding ammonia compounds has no pharmacological significance is not credible.

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The tobacco industry comment also asserts that significant quantities of ammonia compounds are needed to raise the pH of smoke from 6.0 to 7.5 or 8.0. However, no scientific support is provided for this assertion. Moreover, even if the assertion were correct, it would be largely irrelevant. Significantly smaller increases in smoke pH are likely to have the pharmacological effects described above. As noted above, for instance,

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[962] Senkus M (R.J. Reynolds Tobacco Co.), *Some Effects of Smoking* (1976/1977), at 7 (emphasis added). *See* AR (Vol. 700 Ref. 593).

[963] BATCO, *Further Work on 'Extractable' Nicotine*, Southampton, England (1966), at 7. *See* AR (Vol. 62 Ref. 308).

[964] *Id.* at 9.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

documents from RJR conclude that simply increasing the pH of smoke from 6.0 to 6.5 is sufficient to increase the absorption of nicotine in the mouth.[965]

The Agency further disagrees with the tobacco industry comment that the pH of cigarette tobacco has no bearing on the efficiency of nicotine transfer from the tobacco to the smoke. It is a basic scientific principle that compounds in free or unbound forms are vaporized more readily than compounds bound together in salts.[966] Studies of cocaine, for instance, show that when cocaine is bound as a salt (as in cocaine hydrochloride), much of the cocaine is degraded during pyrolysis; in contrast, when the cocaine is converted to "free" form, the transfer of the cocaine to the smoke is much greater.[967] The tobacco industry comment provides no evidence to refute these basic scientific principles or to rebut the evidence in the record showing that the conversion of nicotine from its bound form to its free form increases the transfer of nicotine to smoke.[968]

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[965] Senkus M (R. J. Reynolds Tobacco Co.), *Some Effects of Smoking* (1976/1977), at 7 (emphasis added). *See* AR (Vol. 700 Ref. 593).

[966] Morrison RT, Boyd RN, *Organic Chemistry*, 2d ed., 1966, in Barnett G, Chiang CN eds., *Pharmacokinetics and Pharmacodynamics of Psychoactive Drugs*, A Research Monograph, Biomedical Publications, 2d edition, 1985, at 26. *See* AR (Vol. 711 Ref. 19).

[967] Cook CE, Jeffcoat AR, Perez-Reyes M, Pharmacokinetic studies of cocaine and phencyclidine in man, in Barnett G, Chiang CN eds., *Pharmacokinetics and Pharmacodynamics of Psychoactive Drugs, A Research Monograph*, Biomedical Publications, 2d edition, 1985, at 64-65. *See* AR (Vol. 711 Ref. 16).

[968] After the close of the comment period, FDA received a series of RJR documents from the 1970's regarding the effect of pH adjustments on nicotine delivery. These documents had been made public in a lawsuit involving RJR. Although not necessary to FDA's analysis, these documents provide further confirmation that cigarette manufacturers raise the pH of cigarette smoke to increase the amount of "free nicotine" that is delivered to the smoker, and that this increase in "free nicotine" has a pharmacological effect. One of these documents describes RJR's finding that the pH level of Marlboro and Kool cigarettes had risen significantly, with corresponding increases in "free" nicotine deliveries, and in sales. Teague CE (RJR), *Implications and Activities Arising from Correlation of Smoke pH with Nicotine Impact, Other Smoke Qualities, and Cigarette Sales*, at 1-3. *See* AR (Vol. 711 Ref. 47). The document states:

> In essence, a cigarette is a system for delivery of nicotine to the smoker in attractive, useful form. At "normal" smoke pH, at or below about 6.0, essentially all of the smoke nicotine is chemically combined with acidic

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

substances hence is non-volatile and relatively slowly absorbed by the smoker. *As the smoke pH increases above about 6.0, an increasing proportion of the total smoke nicotine occurs in "free" form, which is volatile, rapidly absorbed by the smoker, and believed to be instantly perceived as nicotine "kick."*

Id. at 2 (emphasis added). The document continues:

> As a result of its higher smoke pH, *the current Marlboro, despite a two-thirds reduction in smoke "tar" and nicotine over the years, calculates to have essentially the same amount of "free" nicotine in its smoke as did the WINSTON.* Over the same period, with some reduction in smoke pH and about two-thirds reductions in smoke "tar" and nicotine, the calculated amount of "free" nicotine in WINSTON smoke has decreased by about two-thirds. *Thus, currently the calculated amount of "free" nicotine in Marlboro smoke is almost three times the amount in WINSTON smoke.*

Id. (emphasis added; underscoring in original). This document goes on to describe methods of increasing smoke pH:

> Methods which may be used to increase smoke pH and/or nicotine "kick" include: (1) increasing the amount of (strong) burley in the blend, (2) reduction of casing sugar used on the burley and/or blend, (3) use of alkaline additives, usually ammonia compounds, to the blend, (4) addition of nicotine to the blend, (5) removal of acids from the blend, (6) special filter systems to remove acids from or add alkaline materials to the smoke, and (7) use of high air dilution filter systems. Methods 1-3, in combination, represent the Philip Morris approach, and are under active investigation.

Id. at 4.

A document entitled "Outline for Smoke pH Presentation" presents further data on the increase in pH in Marlboro cigarettes and Kool cigarettes. Finding that, as compared to RJR's Winston brand, Marlboro cigarettes had several characteristics, including alkaline stem additives and ammonia-puffed leaf, "all combining to raise smoke pH," the presentation states:

> We must conclude that the difference between Marlboro and Winston must be deliberate. . . . What we are seeing and measuring fits what we know about Philip Morris and Brown and Williamson product philosophies. They appear to design products primarily to deliver optimum nicotine impact and satisfaction--aiming also at a relatively bland smoke, letting flavor fall where it will.

Another document in the series is a memorandum to RJR's Director of Marketing and Planning recommending the development of a new "youth-appeal" brand with more tar and nicotine. Colby FG, *Cigarette Concepts to Assure RJR a Larger Segment of the Youth Market* (Dec. 4, 1973). *See* AR (Vol. 711 Ref. 47). According to the memorandum, "any desired additional nicotine 'kick' could be easily obtained through pH regulation."

When these documents were made public, RJR officials responded that the documents are not important and that subsequent studies on Marlboro showed that pH levels between 1973 and 1988 declined, while sales remained steady or increased. Weinstein H, Documents tie nicotine levels, cigarette sales, *Los Angeles Times*, A1 (May 23, 1996). *See* AR (Vol. 711 Ref. 18).

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Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

2. Comments from the tobacco industry argue that ammonia compounds are added to tobacco to enhance the flavor characteristics of cigarette smoke and bind the tobacco together, but not for their effect on nicotine. The Agency disagrees with this comment. The record contains numerous internal documents that indicate that the effect of adding ammonia compounds is to change the delivery or absorption of nicotine. For instance, the Brown & Williamson's 1991 leaf blending manual states that "*[a]mmonia, when added to a tobacco blend, reacts with the indigenous nicotine salts and liberates free nicotine.*"[969] Similarly, William Farone, the former director of applied research at Philip Morris, states that "*[t]he use of ammonia chemistry was important to the industry in maintaining adequate nicotine delivery to satisfy smokers.*"[970] The industry's assertion that the use of ammonia is simply for taste and binding cannot be reconciled with this evidence. Even if ammonia does have a flavor component, this fact does not negate the evidence in the record regarding ammonia's effect on nicotine.

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The tobacco industry cites the addition of ammonia compounds to foods as evidence of ammonia's role in flavor. The use of ammonia compounds in foods, however, is not dispositive evidence of the use of ammonia compounds in tobacco, because the ammonia compounds in cigarettes are burned and inhaled rather than ingested. Moreover, one of the recognized uses for ammonia compounds in foods is "pH control," 21 CFR

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[969] *Regulation of Tobacco Products (Part 3): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess., 21 (Jun. 21, 1994) (statement of David Kessler) (emphasis added). *See* AR (Vol. 709 Ref. 3).

[970] Farone WA. *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 13 (emphasis added). *See* AR (Vol. 638 Ref. 2).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

184.1133–184.1143, which is the same use of ammonia compounds described in the internal tobacco company documents.

3. Comments from the tobacco industry argue that FDA has taken a contradictory position in the Jurisdictional Analysis by finding both that cigarette manufacturers add ammonia compounds to increase the pH of tobacco and that cigarette manufacturers add acids to reduce the harshness of smoke.

FDA's positions are not inconsistent. The Jurisdictional Analysis found, based on the evidence then available, that when manufacturers use tobaccos that produce naturally high pH levels in smoke or that have naturally high nicotine contents, the manufacturers sometimes face the problem that the cigarette smoke contains too much nicotine and is too harsh. In these situations, the record indicates that manufacturers have developed ways to reduce harshness, including lowering pH. *See* Jurisdictional Analysis, 60 FR 41711–41713. In other situations, manufacturers face the opposite problem of cigarette smoke that may not deliver enough nicotine. In these latter situations, the record indicates that manufacturers will enhance nicotine deliveries, including adding ammonia compounds to raise the pH of the tobacco and the smoke, which increases the delivery of free nicotine to the smoker. *See* section II.C.4.c.

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4. Brown & Williamson makes two comments regarding chemical manipulation. First, Brown & Williamson asserts that its internal documents show its knowledge that pH level does not affect nicotine delivery. Second, Brown & Williamson asserts that its internal documents show that the addition of ammonia compounds is simply a booster of smoke "impact."

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

II.C.6.

The Agency disagrees with Brown & Williamson's characterization of its documents. Contrary to Brown & Williamson's comment, the administrative record shows that researchers working for Brown & Williamson and Brown & Williamson's parent, BATCO, have consistently understood that pH levels affect nicotine delivery. As early as 1968, BATCO researchers wrote that "*[n]icotine retention appears to be dependent principally on smoke pH and nicotine content.*"[971] *See* sections II.C.3.c.i., II.C.3.c.iv., II.C.4.c.

In fact, one of the documents cited by Brown & Williamson contradicts its assertion. In a passage not quoted by Brown & Williamson, the document refers to the "*pH dependent effect of nicotine*," further underscoring the company's understanding of the relationship between pH and nicotine.[972]

The Agency does agree with Brown & Williamson that the 1991 blenders handbook links the addition of ammonia compounds to the "impact" of smoke. However, the document makes it clear that "impact" is simply a surrogate term for nicotine delivery, stating that the ammonia compounds increase "the ratio of extractable nicotine to bound nicotine in the smoke"; that "extractable nicotine contributes to the impact in cigarette smoke"; and that "this is how ammonia can act as an impact booster."[973]

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[971] BATCO, *The Retention of Nicotine and Phenols in the Mouth* (1968), at BW-W2-11691 (emphasis added). *See* AR (Vol. 445 Ref. 7593).

[972] Ayres CI (BATCO), Notes from the GR&DC Nicotine Conference, in Proceedings of the Smoking Behaviour-Marketing Conference, Session III (Jul. 9-12, 1984), at BW-W2-02642 (emphasis added). *See* AR (Vol. 12 Ref. 172).

[973] *Regulation of Tobacco Products (Part 3): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 21 (Jun. 21, 1994) (statement of David Kessler). *See* AR (Vol. 709 Ref. 3).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

iv. Comments on Flavorings and Casings.

1. The cigarette manufacturers dispute that flavorings and casings are sometimes used to mask the unpleasant sensory characteristics of nicotine in cigarettes. The tobacco industry claims that flavorings and casings are used solely to affect the flavor and aroma of the cigarette.

The Agency agrees that flavorings and casings influence flavor. Nevertheless, the record shows that these ingredients have another use—that of masking the flavor of harsh high-nicotine tobaccos. In the Jurisdictional Analysis, the Agency cited several pieces of evidence showing that flavorings and casings are used to mask nicotine. *See* 60 FR 41711–41714. For instance, a "flavorist" for RJR wrote that "in air-cured tobaccos (cigar, burley, Maryland), the pH of smoke is generally alkaline and the flavor effect of nicotine is a 'harshness' which can be choking and unpleasant."[974] In these tobaccos, according to the flavorist, "the effect of nicotine is greatly modified, and the harshness is dramatically reduced. . . . by addition of sugars . . . to 'mellow' the smoke."[975] None of this evidence is rebutted by the cigarette manufacturers.

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In addition, the statement of William Farone, the former director of applied research at Philip Morris, confirms that flavorings are used to mask the harshness of nicotine. According to Farone's statement:

> *The tobacco industry found that in the manipulation of the nicotine/tar ratio, the methods used to increase the nicotine to tar ratio sometimes resulted in a cigarette that was too harsh.* With a standard nicotine/tar ratio in a traditional cigarette no flavor smoothing compounds are generally needed to produce a

[974] Leffingwell JC, Nitrogen components of leaf and their relationship to smoking quality and aroma, *Recent Advances in Tobacco Science*, vol. 2, at 9. *See* AR (Vol. 28 Ref. 450).

[975] *Id.*

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

palatable cigarette. The higher tar levels in traditional cigarettes mask the harshness of nicotine and the associated compounds produced in higher nicotine to tar ratios. A low tar cigarette with a higher nicotine/tar ratio than a traditional cigarette could be very harsh due to the lack of sufficient specific tar components to mask the nicotine and related basic compounds. *To overcome the harshness due to the increased burley in the blend, the industry used flavor "smoothers."*[976]

Thus, the evidence in the record supports the finding in the Jurisdictional Analysis that the cigarette industry sometimes uses flavorings to mask the harshness of nicotine in cigarettes with nicotine-rich tobacco blends.

2. The cigarette manufacturers cite the use of menthol in cigarettes as evidence that they do not use flavorings to mask the effects of nicotine. According to the industry, menthol is not used to mask the effects of high-nicotine tobaccos because menthol cigarettes generally have nicotine yields that are lower than or equal to regular cigarettes.

The Agency rejects this argument. The evidence before the Agency indicates that flavorings like cocoa, sugars, and licorice, which produce acids in smoke, are used to mask the bitterness or harshness of nicotine. *See* Jurisdictional Analysis 60 FR 41711–41714. The evidence does not indicate that menthol is used to mask harshness of tobacco. Consequently, the data presented by the industry on menthol is irrelevant to whether other flavorants are used to mask nicotine.

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v. Comments on the Consistency of Nicotine Deliveries.

1. The cigarette manufacturers argue that the ability to produce cigarettes with uniform and consistent levels of nicotine is not evidence of any "intended use." They

[976] Farone WA. *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 14-15 (emphasis added). *See* AR (Vol. 638 Ref. 2).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

assert that blending to achieve consistency is a common practice among manufacturers that make consumer goods from agricultural products.

However, the remarkable degree of consistency in nicotine deliveries achieved by the manufacturers is especially relevant to the issue of the manipulation and control of nicotine. As discussed in section II.C.4.e.iii., above, the manufacturers' precise control over nicotine deliveries refutes the manufacturers' assertion that "the companies do not independently 'control' for or 'manipulate' the nicotine content in any of their blends."[977] Moreover, the manufacturers' precise control over nicotine deliveries is consistent with—and corroborates—the Agency's finding that manufacturers intend that cigarettes will be used for pharmacological purposes. As discussed in the Jurisdictional Analysis, an FDA laboratory study showed that nicotine delivery varies so little from lot to lot of cigarettes that it equals or exceeds the degree of control exercised by pharmaceutical companies over the active ingredients in prescription drugs.[978] The manufacturers' precise control over nicotine deliveries enable the industry to ensure that consumers can use cigarettes to satisfy addiction or to obtain other pharmacological effects.

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vi. Comments on Breeding.

The comments of the cigarette industry claim that the cigarette manufacturers do not manipulate nicotine through plant breeding or agronomic practices. While the comments make several valid points on tangential issues, they do not affect the basic conclusions made in the Jurisdictional Analysis.

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[977] Joint Comment of Cigarette Manufacturers, Comment (Jan. 2, 1996), Vol. V, at 66. *See* AR (Vol. 535 Ref. 96).

[978] FDA, Center for Drug Evaluation and Research, Division of Drug Analysis, Memorandum on Analysis of Packages of Cigarettes (Apr. 4, 1994). *See* AR (Vol. 29 Ref. 487).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

1. Regarding FDA's contention that American-grown tobaccos have had increasingly high levels of nicotine since the mid 1950's, the comments fault FDA for singling out the years 1955 and 1980 for comparison.

The Agency reported in the Jurisdictional Analysis the change in nicotine content between 1955 and 1980 because those were the years analyzed in the paper by DeJong cited by the Agency.[979] The Agency agrees that the more recent data from the North Carolina Official Variety Trials, as submitted by the comments, show that nicotine content of leaves from that area has leveled off since 1980, and that the last 17 years appear to show a decrease in nicotine levels.[980] The Agency does not agree, however, that it should have compared nicotine levels in the 1950's to nicotine levels in 1989, as suggested by the cigarette manufacturers. Unusually low nicotine levels were recorded in 1989 when compared with the five years preceding and succeeding it.

Other articles and information support the Agency's contention that the nicotine content of domestic tobacco increased from the 1950's to 1980. For example, one study cited by a comment concluded that nicotine levels "changed dramatically" from the mid-1950's to the early 1980's and ascribed the increase to changes in production practices.[981]

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[979] DeJong DW, The role of American tobacco leaf chemistry in low-yield cigarettes: an agricultural viewpoint. *Tabak Journal International*. May 1985:376-383. *See* AR (Vol. 27 Ref. 401).

[980] Joint Comment of Cigarette Manufacturers, Comment (Jan. 2, 1996), Vol. IV, at 18. *See* AR (Vol. 535 Ref. 96).

[981] Bowman DT, Wernsman EA, Corbin TC, *et al.*, Contribution of genetic and production technology to long-term yield and quality gains in flue-cured tobacco, *Tobacco Science* 1984;28:30-35, at 34-35. *See* AR (Vol. 535 Ref. 96, vol. IV.A).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

In addition, Earl Wernsman of North Carolina State University told the Agency that nicotine levels have increased over the past 30 years.[982]

The Agency, however, does not agree with the industry's claim, that "FDA's reliance on the DeJong data, together with the Agency's total failure to acknowledge contrary data from equally or more authoritative sources, reflects a general strategy of selective and biased citation from the scientific literature."[983] In fact, both sets of data reflect rising nicotine levels in tobacco from the mid 1950's through 1980.

2. The cigarette industry comments assert that the manufacturers have rejected high-nicotine tobacco crops produced during drought years. According to the industry, this rejection of high-nicotine crops shows that the manufacturers do not seek to manipulate nicotine through breeding high-nicotine tobaccos.

The Agency does not agree that any reliable inference can be drawn from the rejection of tobacco crops in drought years. This evidence establishes only that nicotine content can on occasion rise too high for the manufacturers' use. The Agency has never maintained that nicotine levels could not reach excessive levels. To the contrary, as discussed in the Jurisdictional Analysis, the Agency recognizes that too much nicotine in a cigarette can make the cigarette too harsh, requiring the use of flavors and casings to mask the harshness. *See* 60 FR 41712–41713.

3. The cigarette industry comments raise a number of issues regarding FDA's discussion of the Minimum Standards Programs (MSP's). The comment claims that

[982] Memorandum of Mar. 22, 1994, teleconference, from Murray M. to Wernsman E (Mar. 23, 1994). *See* AR (Vol. 256 Ref. 3459).

[983] Joint Comment of Cigarette Manufacturers, Comment (Jan. 2, 1996), Vol. IV, at 9. *See* AR (Vol. 535 Ref. 96).

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"FDA has mischaracterized the nature, purpose and effect of the . . . MSP's by claiming that the MSP's were designed to ensure that nicotine levels did not fall below a specified level," and that by "minimizing the role of the USDA, tobacco breeders, and State Extension-Research Services, FDA mischaracterizes the tobacco industry's participation in these programs as 'controlling.'"[984] The comment argued that the cigarette manufacturers do not control the MSP's, that the MSP's are not designed to maintain nicotine above a specified level, and that the MSP's prevent the introduction of high-nicotine varieties into cultivation.

The Agency does not find compelling any of the arguments raised by the comment that were intended to dispute the two most significant findings of the Agency regarding MSP's: that they are used to ensure that nicotine levels do not fall below a specified level, and that the cigarette manufacturers are active participants in the program.

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The comment points out that there are a variety of purposes of the MSP's, and argues that therefore it is incorrect for FDA to claim that their purpose is "to ensure that nicotine levels in marketed tobacco do not fall below specified levels."[985] FDA agrees that the MSP's have purposes in addition to controlling nicotine levels. However, the fact remains that the MSP's help ensure that nicotine levels in marketed tobacco do not fall below the level in acceptable tobacco varieties. DeJong made this point clear when he wrote that "the first minimum standards programme was initiated in 1964. . . . Discount or *low-nicotine cultivars had previously been declared outside the price support* system."[986]

[984] AR at 18-19 (emphasis added).

[985] *Id.* at 21-22.

[986] DeJong DW. The role of American tobacco leaf chemistry in low-yield cigarettes: an agricultural viewpoint, *Tabak Journal International*, May 1985:382 (emphasis added). *See* AR (Vol. 27 Ref. 401).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

FDA's point, which is not disputed by the comment, is that the discount and MSP programs discourage the planting of varieties that accumulate unusually low levels of nicotine.

FDA believes that it appropriately characterized the industry's role in the MSP's. The agency noted that the MSP's are administered by the USDA. *See* Jurisdictional Analysis, 60 FR 41697. In stating that the manufacturers exert control over the MSP's, the Agency did not imply that they exert sole control over all aspects of the programs. The manufacturers do, however, each have a vote on the MSP committees that set up the rules and administer the programs. They also represent by far the largest economic bloc on those committees.

4. The cigarette industry asserts that the cigarette manufacturers do not control the agronomic practices used by tobacco farmers for the purpose of increasing the nicotine content of tobacco. The comment maintains that all of the agronomic practices cited by the Agency as raising nicotine levels provide significant advantages to the farmer completely independent of any nicotine-enhancing properties. The comment also notes that some agronomic practices, such as irrigation, decrease nicotine content, and that recommendations regarding other practices, such as decreasing the use of nitrogen from the very high levels that were used for a few years, also result in decreased nicotine levels.

The Agency generally agrees with the comment on these points. The Agency never stated, and did not mean to imply, that cigarette manufacturers exert direct control over tobacco farmers or breeders. The Agency also agrees that farmers do not use nicotine-elevating agricultural practices exclusively for the purpose of elevating nicotine levels. The Agency is aware that farmers choose the agricultural practices they use for a

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variety of purposes. Nevertheless, DeJong noted that "[h]eavy application of nitrogen fertilization, early topping and tight chemical sucker control all acted in concert to push alkaloid levels upward."[987]

In any case, the Agency's fundamental point regarding tobacco breeding and farming is that tobacco leaves sold in the U.S. contain adequate levels of nicotine to enable the manufacturers to maintain nicotine delivery in their products at the levels they choose. When, in the early and mid-1950's, farmers grew a preponderance of low-nicotine tobaccos, programs were set up to ensure that farmers would no longer grow such tobaccos. Since that time, manufacturers have had no difficulty purchasing tobaccos that provide the levels of nicotine that they need for their products. And in at least one well-documented case, Brown & Williamson doubled the nicotine content of one variety of flue-covered tobacco as a "blending tool" for use in low-tar cigarettes. This "Y-1" tobacco was designed to enable the company to maintain nicotine levels while lowering the tar content of cigarettes. *See* section II.C.3.c.iii., above.

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vii. Comments on Leaf Purchasing.

1. The cigarette manufacturers assert that over time there has been no increase in the nicotine content of the tobacco they purchase. The manufacturers argue this is evidence that they do not use nicotine content as a principal factor in leaf selection.

The Agency disagrees with the manufacturers' factual assertion regarding trends in nicotine content. The evidence in the record indicates that the nicotine content has increased in the tobacco purchased by cigarette manufacturers. As pointed out in the

[987] *Id.*

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

Jurisdictional Analysis, the nicotine content in American tobaccos of all types has increased since the 1950's. 60 FR 41696–41697. Moreover, a 1978 article submitted by the Tobacco Institute and entitled "Genetic Manipulation for Tailoring the Tobacco Plant To Meet the Requirements of the Grower, Manufacturer, and Consumer" states that "*[i]n the United States the demand for lower stalk flue-cured tobacco has decreased.*"[988] This confirms the existence of a trend first described by USDA officials in congressional testimony in the late 1950's. *See* section II.C.4.a.i., above. At that time USDA indicated that the tobacco industry had "moved up the stalk" in blending tobaccos by using the higher nicotine leaves in the upper part of the tobacco plant.[989]

2. The cigarette manufacturers also assert that they have rejected high-nicotine tobaccos. Again, they claim that this is evidence that they do not use nicotine content as a principal factor in leaf selection.

The Agency disagrees with the manufacturers' argument. As noted above in section II.C.6.c.vi., the Agency recognizes that too much nicotine in a cigarette can make the cigarette too harsh.

3. In its comments, Brown & Williamson disputes that it regularly adjusts the stalk position of its leaf purchases during the buying season based upon the results of nicotine analyses. The company's response, however, conflicts with the information

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[988] Chaplin JF, Genetic manipulation for tailoring the tobacco plant to meet the requirements of the grower, manufacturer, and consumer, *Bulletin D'Information Coresta* 1978;17-32, at 21 (emphasis added). *See* AR (Vol. 535 Ref. 96).

[989] *Hearings on False and Misleading Advertising (filter-tip cigarettes), Subcommittee on Government Operations, U.S. House of Representatives*, 85th Cong. 1st Sess. 189 (Jul. 1957). See AR (Vol. 172 Ref. 2035).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

provided to FDA by company employees during FDA's May 1994 visit to Brown & Williamson. *See* Jurisdictional Analysis, 60 FR 41705. Moreover, Brown & Williamson provides no affidavits or other documentary evidence to support its comment.

viii. Comments on Reconstituted Tobacco.

1. The cigarette manufacturers assert that they do not use reconstituted tobacco to manipulate or control nicotine levels. As evidence of this point, they argue that nicotine levels in reconstituted tobacco are lower than those in most tobacco blends.

The Agency disagrees with the argument. Evidence in the record shows that reconstituted tobacco is used by cigarette manufacturers as a site for the addition of ammonia compounds. According to an article in the *Wall Street Journal*, an internal Brown & Williamson handbook describes the "nicotine pick-up potential" of ammonia in reconstituted tobacco.[990] The article also states that ammonia added to reconstituted tobacco can scavenge nicotine from the tobacco in the rest of the cigarette, significantly increasing the level of "free nicotine" in the cigarette.

2. The cigarette manufacturers assert that they do not closely monitor and control the level of nicotine in reconstituted tobacco.

The Agency disagrees with this assertion. The record shows that finished cigarettes contain precisely controlled and consistent nicotine levels. *See* Jurisdictional Analysis, 60 FR 41732. Because reconstituted tobacco is a significant ingredient in finished cigarettes, the precise control over nicotine in the finished cigarettes could not be

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[990] Freedman AM. Tobacco firm shows how ammonia spurs delivery of nicotine, *Wall Street Journal* (Oct. 18, 1995), A1. *See* AR (Vol. 639 Ref. 2).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

achieved unless the manufacturer also precisely controlled the nicotine level in reconstituted tobacco. Without such precise control, the wide variations in the nicotine levels of the tobacco stems and other raw ingredients of reconstituted tobacco would produce significant variations in the nicotine content of reconstituted tobacco and the finished cigarettes.

ix. Other Comments.

1. The Agency found in the Jurisdictional Analysis, based on the evidence then available, that cigarette manufacturers sometimes increase the degree to which the "tipping paper," which is wrapped around the filter, is extended over the tobacco rod. *See* 60 FR 41721. One study cited by the Agency reported that this increased "overwrap" reduced the nicotine deliveries reported by the FTC testing method (because the test protocol requires stopping the test when the cigarette is smoked to within 3 millimeters of the tipping paper), while allowing smokers to increase their nicotine intake above the reported levels (by smoking the tobacco under the overwrap).[991]

The manufacturers raise a number of questions about the data on which FDA relied and seek to depict FDA's discussion of the overwrap width as speculative. In most cases, however, the information that would answer the questions raised by the manufacturers is within their control, but is nevertheless not provided.

[991] Grunberg NE, Morse DE, Maycock VA, *et al.*. Changes in overwrap and butt length of American filter cigarettes. *NY State Journal of Medicine* Jul. 1985;310-312. *See* AR (Vol. 29 Ref. 478).

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Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

For example, the manufacturers argue that smokers do not smoke the overwrap because it is unpalatable, but they do not provide evidence to support this assertion despite the fact that the extensive consumer testing conducted by the manufacturers undoubtedly provides the information necessary to resolve whether the overwrap is smoked and whether it is palatable. The manufacturers also argue that the increase in overwrap width found in many cigarettes would not increase the amount of nicotine available to smokers if the burn rate of the cigarette were simultaneously increased. The burn rate of cigarettes is information known to the cigarette manufacturers but not to FDA. Yet the manufacturers fail to provide information on burn rate that would permit resolution of the issue they raise.

Moreover, although the manufacturers deny that the overwrap has been widened to increase availability of nicotine, they offer no alternative explanation for the increase found in the study relied on by FDA. In light of the ease with which the manufacturers could have provided the information necessary to show that the overwrap is not used to provide elasticity, and their failure to provide it, FDA concludes that the evidence supports the finding made in the Jurisdictional Analysis. Nevertheless, only additional information can help determine whether an increase in the tipping paper reduces the accuracy of the FTC measurement.

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2. The cigarette manufacturers assert that the fact that they may hold patents permitting them to carefully manipulate and control nicotine does not prove that they actually do so. They also argue that patents are submitted by individual employees and that, as such, they are not evidence of the company's intentions.

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

FDA cited the multitude of patents held by tobacco manufacturers on methods of manipulating nicotine delivery as additional evidence that the manufacturers have engaged in extensive research to develop methods to optimize nicotine delivery. The fact that the manufacturers have invested considerable resources in developing means of manipulating and controlling nicotine deliveries, including developing and acquiring patents, demonstrates that the manufacturers seek to be able to manipulate and control nicotine deliveries and have in fact "designed" and "planned" methods of doing so. This evidence is relevant to establishing the manufacturers' intentions. In light of the large number of patents held by the industry with the common goal of manipulating nicotine delivery, the argument that all of these patents were obtained by individual employees working without the direction of the manufacturers is not credible.

3. In the Jurisdictional Analysis, the Agency found that the failure of the cigarette manufacturers to remove nicotine from cigarettes was evidence that the manufacturers intend their products to provide the pharmacological effects of nicotine. *See* 60 FR 41779–41787. In their comments, however, the cigarette manufacturers assert that they do not have the capacity to manufacture an acceptable denicotinized cigarette and, even if they did, this would not establish that the manufacturers intend to affect the structure or function of the body.

In the Agency's view, the failure of denicotinized cigarettes in the marketplace is further evidence of the essential role of nicotine in cigarettes. The fact that efforts to introduce denicotinized cigarettes have failed demonstrates that consumers smoke cigarettes primarily to obtain the pharmacological effects of nicotine. Moreover, evidence that a manufacturer has, but does not use, technology that could remove a

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pharmacologically active ingredient from its product is relevant evidence that the manufacturer intends that the product will have pharmacological effects upon consumers.

The manufacturers' assertion that denicotinized cigarettes have failed because of inadequacies in the denicotinizing technologies is not supported by the evidence in the record. To the contrary, the record contains abundant evidence that the reason a denicotinized cigarette will not succeed is because it fails to provide the pharmacological effects sought by consumers. For instance, an RJR document asserts that "*a zero nicotine cigarette . . . really has no potential to provide smoking satisfaction.* It produces no taste in the mouth, but even more seriously *it fails to provide the ultimate satisfaction in the lungs.*"[992]

4. The cigarette manufacturers argue that the evidence in the administrative record does not establish that they add "extraneous" nicotine to cigarettes. According to the manufacturers, the failure of the Agency to demonstrate that they add extraneous nicotine means that the Agency has not demonstrated that the manufacturers manipulate and control nicotine.

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The Agency disagrees. The administrative record contains abundant evidence that tobacco manufacturers can manipulate and control nicotine deliveries without adding extraneous nicotine. The record before the Agency demonstrates that the manufacturers have developed and used many techniques to manipulate and control nicotine, and few of them involve the addition of extraneous nicotine. These techniques are discussed in detail in section II.C.4., above and include using nicotine-rich blends in low-yield cigarettes,

[992] Senkus M (R.J. Reynolds Tobacco Co.), *Some Effects of Smoking* (1976/1977), at 9 (emphasis added). *See* AR (Vol. 700 Ref. 593).

Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

using filtration and ventilation techniques that selectively remove more tar than nicotine, and chemical manipulation to increase free nicotine deliveries. All of these techniques manipulate and control nicotine deliveries; all of them facilitate consumer use of cigarettes for pharmacological purposes; and none of the techniques require the addition of extraneous nicotine.

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Source: https://www.industrydocuments.ucsf.edu/docs/fsmm0000

D. THE STATEMENTS, RESEARCH, AND ACTIONS OF THE SMOKELESS TOBACCO MANUFACTURERS SHOW THAT THE MANUFACTURERS INTEND THEIR PRODUCTS TO AFFECT THE STRUCTURE AND FUNCTION OF THE BODY

In sections II.A. and II.B., above, the Agency concluded that smokeless tobacco is "intended" to affect the structure and function of the body on the basis of the foreseeable pharmacological effects and uses of smokeless tobacco and its widespread actual use by consumers for pharmacological purposes. In this section, the Agency considers a third category of evidence of intended use: the statements, research, and actions of the smokeless tobacco manufacturers.

The administrative record includes considerable evidence of the smokeless tobacco manufacturers' statements, research, and manufacturing practices. Much of this evidence has only recently become available as the result of the Agency's investigation, congressional hearings, and other investigations and sources. As discussed in section II.C.1., above, this evidence of the statements, research, and actions of the manufacturers is part of the relevant objective evidence that the Agency may rely upon in determining a product's "intended uses." The Agency's role in making these determinations is that of a fact finder. The Agency's fact-finding task has been made more difficult by the manufacturers' general refusal to cooperate with the Agency's investigation. In particular, the manufacturers failed to provide FDA with information and documents requested by the Agency in July 1994 regarding the role of nicotine in smokeless tobacco.[993] This lack of cooperation has made the Agency's investigation more difficult. The limited number of company documents provided by the

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[993] *See*, e.g., Letter from Chesemore RG (FDA) to Gierer V (U.S. Tobacco Company) Jul. 19, 1994. *See* AR (Vol. 54 Ref. 619).

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manufacturers with their comments sheds little light on the role of nicotine in smokeless tobacco and does not significantly change the evidence in the record.

The Agency made extensive findings based on the evidence then before it regarding the statements, research, and actions of the smokeless tobacco manufacturers in the Jurisdictional Analysis. The Agency received comments on these findings from the tobacco industry, public health organizations and other groups and members of the public. After careful consideration of the evidence in the record and the public comments, the Agency finds that the evidence provides an independent basis for concluding that smokeless tobacco is in fact intended to affect the structure and function of the bodies of smokeless tobacco users.

As described in this section, the evidence from internal company documents and other sources shows that smokeless tobacco manufacturers: (1) know that nicotine has pharmacological effects and uses, including causing and sustaining addiction; and (2) manipulate and control the delivery of nicotine from smokeless tobacco in a manner that promotes tolerance and addiction in consumers. Indeed, in the case of the nation's largest smokeless tobacco manufacturer, the statements of senior officials and the company's marketing strategies reveal that the company relies on an explicit "graduation process," under which users of smokeless tobacco are encouraged to progress from "starter" products that deliver low levels of nicotine to products that deliver higher and more addictive levels of nicotine. The cumulative evidence shows that the manufacturers design smokeless tobacco with an intent to affect the structure and function of the body.[994]

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[994] The discussion of the statements, research, and actions of the manufacturers in this section cites many documents. It is the totality of the evidence from these documents that the Agency relies upon. No single document cited by the Agency is essential to the Agency's conclusion that the manufacturers intend their

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1. The Smokeless Tobacco Manufacturers Understand That Nicotine Has Addictive and Other Pharmacological Effects and That Consumers Use Smokeless Tobacco To Obtain these Effects

Extensive evidence in the administrative record, including statements and research of smokeless tobacco manufacturers, demonstrates that the manufacturers know that nicotine causes significant pharmacological effects, including addiction. These statements and research also demonstrate that the manufacturers understand that consumers use smokeless tobacco to obtain the pharmacological effects of nicotine.

For example, Brown & Williamson Tobacco Corporation, which is also a smokeless tobacco manufacturer,[995] understands that nicotine is addictive; that nicotine has other significant pharmacological effects; and that consumers use tobacco products to obtain nicotine. *See* section II.C.2.c., above. Researchers for Brown & Williamson's parent corporation, BATCO, have long regarded "buccal administration of nicotine" through products such as chewing tobacco and wet snuff as alternatives to the delivery of nicotine through cigarettes.[996] According to these researchers, these types of tobacco usage—smoking, chewing, and snuffing—allow nicotine to go directly into the blood and to the brain; they stated that "[t]he common factor in all the types of tobacco usage . . . is nicotine,

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products to affect the structure and function of the body. In particular, none of the documents in the Agency's docket of confidential documents is essential to the Agency's determination. *See* AR (Vols. 505-518).

[995] Valero G. Most poised to overtake leaf smokeless tobacco, *U.S. Distribution Journal*, Dec. 15, 1995; 222(12):12. *See* AR (Vol. 711 Ref. 22).

[996] Minutes of B.A.T. Group Research Conference at St. Adele, Quebec (Nov. 9-13, 1970), at 3. *See* AR (Vol. 44 Ref. 15-2).

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either absorbed through the lungs *or the lining of the nose or mouth.* Taken in these ways *nicotine will quickly enter a direct route, in the blood, to the brain.*"[997]

Indeed, as recently as 1992, Brown & Williamson stated that "[t]he fact that people use snuff and chewing tobacco indicates that administration routes other than the inhalation route can deliver tobacco satisfaction."[998] BATCO scientists use "satisfaction" as a euphemism for the pharmacological effects of nicotine, stating "[i]ntuitively it is felt that *'satisfaction' must be related to nicotine.* Many people believe it [is] a 'whole body response' and *involves the action of nicotine in the brain.*"[999] *See* section II.E.2., below.

Similarly, a senior vice president for marketing for United States Tobacco Company (UST), the nation's largest smokeless tobacco manufacturer,[1000] wrote in a memo on new product development that "*virtually all tobacco usage is based upon nicotine, 'the kick,' satisfaction.*"[1001] The executive further stated:

> Nicotine gives the consumer satisfaction. Some would describe it as a pleasant feeling. Others would describe it as a kick. . . . Others would describe it as a relaxing feeling.[1002]

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[997] BATCO Group R&D Conference on Smoking Behaviour at Southampton, England (Oct. 11-12, 1976), at BW-W2-02145 (emphasis added). *See* AR (Vol. 14 Ref. 180-2).

[998] Transdermal Nicotine Patches, at 3. *See* AR (Vol. 531 Ref. 124).

[999] BATCO Nicotine Conference at Southampton, England (Jun. 6-8, 1984) at BW-W2-01977 (emphasis added). *See* AR (Vol. 22 Ref. 287-7).

[1000] UST has 82% of the market for moist snuff products sold in the United States in 1994. It also has nearly 40% of the market for all smokeless tobacco sold in the United States. *See* Valero G, Moist poised to overtake leaf; smokeless tobacco, *U.S. Distribution Journal*, Dec. 15, 1995; 222(12):12. *See* AR (Vol. 711 Ref. 22).

[1001] Deposition of Erik Lindqvist, transcript of jury trial proceedings at 1662 in *Marsee v. U.S. Tobacco*, Civil Action No. 84-2777R (W.D. Ok. 1986) (emphasis added). *See* AR (Vol. 22 Ref. 292).

[1002] *Id.*

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Another UST document compares the nicotine delivery of one of its products, Skoal Bandits, with the nicotine delivery of cigarettes. This document states:

> The nicotine contents are more or less equivalent to that of a good quality cigarette of average strength. The nicotine is absorbed, giv[ing] satisfaction to the smoker.[1003]

Like the major cigarette manufacturers, UST has funded its own studies on nicotine pharmacology, including studies on the absorption of nicotine from snuff and chewing tobacco, the effects of smokeless tobacco on performance and psychophysiological response, and detection of nicotine in blood.[1004] Other UST studies were designed to compare routes of nicotine administration in snuff and cigarette smoking[1005] and to describe the pharmacokinetics of nicotine and its major metabolites in experienced and inexperienced snuff

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[1003] Potential Questions and Answers, submitted in *Marsee v. U.S. Tobacco*, Civil Action No. 84-2777R (W.D. Ok. 1986), at 1. *See* AR (Vol. 30 Ref. 509).

[1004] Kyerematen, GA, Dvorchik, BH, Vesell, ES. Influence of different forms of tobacco intake on nicotine elimination in man, *Pharmacology* 1983;26:205-209. *See* AR (Vol. 119 Ref. 1102).

Landers DM, Crews DJ, Boucher SH, *et al.*, The effects of smokeless tobacco on performance and psychophysiological response, *Medicine and Science in Sports & Exercise* 1992;24(8):895-903, as cited in *Health Effects of Smokeless Tobacco: Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 144 (Nov. 29, 1994). *See* AR (Vol. 710 Ref. 4).

Allen JK, Stern JR, Harris J, *Analysis of Nicotine in Blood by HPLC with Electrochemical Detection, (Abstract)*, submitted for presentation at the 10th International Symposium on Column Liquid Chromatography, San Francisco, CA (May 18-23, 1986), as cited in *Health Effects of Smokeless Tobacco: Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 144 (Nov. 29, 1994). *See* AR (Vol. 710 Ref. 4).

Baldini FD, Skinner JS, Landers DM, *et al.*, Effects of varying doses of smokeless tobacco at rest and during brief, high-intensity exercise, *Military Medicine* 1992;157:51-55, as cited in *Health Effects of Smokeless Tobacco: Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 144 (Nov. 29, 1994). *See* AR (Vol. 710 Ref. 4).

[1005] U.S. Tobacco Company, Results of Comparison of Routes of Nicotine Administration. Plaintiff's exhibit 3.28 from *Marsee v. U.S. Tobacco*, Civil Action No. 84-2777R (W.D. Ok. 1986). *See* AR (Vol. 24 Ref. 318).

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takers.[1006] The study comparing routes of nicotine administration, for instance, found that smokeless tobacco can actually deliver more nicotine than cigarettes to new tobacco users, stating that "for naive tobacco users, bioavailability of nicotine is greater after snuff dipping than after cigarette smoking. . . ."[1007]

UST is also a founding member of the Council for Tobacco Research (CTR).[1008] As discussed in section II.C.2.d., above, CTR has funded many studies on behalf of its members evaluating the pharmacological effects of nicotine on the body. At least one of these studies stated that nicotine in tobacco can cause "drug addiction."[1009] As a member of the Council for Tobacco Research, UST thus had direct knowledge of the pharmacological effects and the consumer uses of nicotine.

[1006] U.S. Tobacco Company, Pharmacokinetics of Nicotine and Its Major Metabolites in Naive and Habituated Snuff Takers. Plaintiff's exhibit 3.27 from *Marsee v. U.S. Tobacco*, Civil Action No. 84-2777R (W.D. Ok. 1986). *See* AR (Vol. 24 Ref. 317).

[1007] U.S. Tobacco Company, Results of Comparison of Routes of Nicotine Administration. Plaintiff's exhibit 3.28 from *Marsee v. U.S. Tobacco*, Civil Action No. 84-2777R (W.D. Ok. 1986). *See* AR (Vol. 24 Ref. 318).

[1008] UST has been intimately connected with CTR since its inception. The minutes of the initial meeting in March 1954 of the Tobacco Industry Research Council, the predecessor of the Council for Tobacco Research, indicate that UST's president was the first vice chairman of the Council. TIRC, Report on Meeting (Mar.15, 1954). *See* AR (Vol. 301 Ref. 4393). Subsequently, UST's president served as a director of CTR from 1976 to 1984. Organization and Function of CTR (summaries of CTR meetings, 1976-1984). *See* AR (Vol. 342 Ref. 5382). Prior to 1988, UST manufactured cigarettes and was a class A member of CTR. Since 1988, UST has been a class B member of CTR. *Health Effects of Smokeless Tobacco: Hearing Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 137 (Nov. 29, 1994). *See* AR (Vol. 710 Ref. 4).

[1009] *See, e.g.*, Svensson TH, Grenhoff J, Engberg G, Effect of nicotine on dynamic function of brain catecholamine neurons, in *The Biology of Nicotine Dependence*, eds. Bock G, Marsh J, *CIBA Foundation Symposium*, 1990;152:169-180. *See* AR (Vol. 61 Ref. 273).

Tung CS, Ugedo L, Grenhoff J, *et al.*, Peripheral infection burst firing in locus coeruleus neurons by nicotine mediated via excitatory amino acids, *Synapse* 1989;4(4):313-318. *See* AR (Vol. 61 Ref. 278).

Rosecrans JA, Nicotine as a discriminative stimulus: a neurobehavioral approach to studying central cholinergic mechanisms, *J Subst Abuse* 1989;1(3):287-300. *See* AR (Vol. 59 Ref. 239).

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II.D.1.

Nicotine's pharmacological effects are also understood by Procordia A.B., the parent of Pinkerton Tobacco Company, the nation's third largest smokeless tobacco manufacturer.[1010] Through corporate subsidiaries, Procordia has extensively investigated the pharmacological effects of nicotine, including funding numerous studies on nicotine's effects on the brain.[1011]

[1010] Valero G, Moist poised to overtake leaf; smokeless tobacco, *U.S. Distribution Journal*, Dec. 15, 1995; 222(12):12. *See* AR (Vol. 711 Ref. 22).

[1011] Procordia owns two foreign smokeless tobacco manufacturers, Svenska Tobaks AB and Swedish Tobacco Co. Through Svenska Tobaks and Swedish Tobacco, Procordia funded the following studies on nicotine pharmacology:

Adem A, Jossan SS, d'Argy R, *et al.*, Distribution of nicotinic receptors in human thalamus as visualized by 3H-nicotine and 3H-acetylcholine receptor autoradiography, *J Neural Transm* 1988;73(1):77-83. *See* AR (Vol. 45 Ref. 10).

Adem A, Nordberg A, Jossan SS, *et al.*, Quantitative autoradiography of nicotinic receptors in large cryosections of human brain hemispheres, *Neurosci Lett* 1989;101(3):247-252. *See* AR (Vol. 45 Ref. 9).

Andersson K, Eneroth P, Agnati L, Nicotine-induced increases of noradrenaline turnover in discrete noradrenaline nerve terminal systems of the hypothalamus and the median eminence of the rat and their relationship to changes in the secretion of adenohypophyseal hormones, *Acta Physiol Scand* 1981;113:227-231. *See* AR (Vol. 273 Ref. 3784).

Andersson K, Fuxe K, Agnati LF, *et al.*, Effects of acute central and peripheral administration of nicotine on ascending dopamine pathways in the male rat brain. Evidence for nicotine induced increases of dopamine turnover in various telencephalic dopamine nerve terminal systems, *Med Biol* 1981;59(3):170-176. *See* AR (Vol. 45 Ref. 11).

Andersson K, Fuxe K, Eneroth P, *et al.*, Interactions of nicotine and pentobarbitone in the regulation of telencephalic and hypothalamic catecholamine levels and turnover and of adenohypophyseal hormone secretion in the normal male rat, *Naunyn Schmiedebergs Arch Pharmacol* 1982;321:287-292. *See* AR (Vol. 423 Ref. 7141).

Andersson K, Hockey GRJ, Effects of cigarette smoking on incidental memory, *Psychopharmacology* 1977;52:223-226. *See* AR (Vol. 125 Ref. 1300).

Biber A, Scherer G, Hoepfner L, *et al.*, Determination of nicotine and cotinine in human serum and urine: an interlaboratory study, *Toxicol Lett* 1987;35(1):45-52. *See* AR (Vol. 140 Ref. 1649).

Crooks J, Adem A, Jacob P, *et al.*, A comparison of the binding of nicotine and nornicotine stereoisomers to nicotinic binding sites in rat brain cortex, *Naunyn Schmiedebergs Arch Pharmacol* 1991;343(2):123-127. *See* AR (Vol. 152 Ref. 1887).

Falkeborn Y, Larsson C, Nordberg A, Chronic nicotine exposure in rat: a behavioral and biochemical study of tolerance, *Drug Alcohol Depend* 1981;8:51-60. *See* AR (Vol. 141 Ref. 1679).

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Fuxe K, Andersson K, Eneroth P, *et al.*, Neurochemical mechanisms underlying the neuroendocrine actions of nicotine: focus on the plasticity of central cholinergic nicotinic receptors, *Prog Brain Res* 1989;79:197-207. *See* AR (Vol. 47 Ref. 95).

Fuxe K, Everitt BJ, Holzfelt T, On the action of nicotine and cotinine on central 5-hydroxytryptamine neurons, *Pharmacol Biochem Behav* 1979;10(5):671-677. *See* AR (Vol. 152 Ref. 1869).

Fuxe K, von Euler G, Fimman UB, *et al.*, Reduction of [3 H]nicotine binding in hypothalamic and cortical membranes by dopamine D1 receptors, *Acta Physiol Scand* 1989;136(2):295-296. *See* AR (Vol. 127 Ref. 1351).

Fuxe K, Agnati LF, Jansson A, *et al.*, Regulation of endocrine function by the nicotinic cholinergic receptor, *CIBA Foundation Symposium* 1990;152:113-130. *See* AR (Vol. 131 Ref. 1450).

Grenhoff J, Aston Jones G, Svensson TH, Nicotinic effects on the firing pattern of midbrain dopamine neurons, *Acta Physiol Scand* 1986;128(3)351-358. *See* AR (Vol. 143 Ref. 1771).

Larsson C, Nordberg A, Comparative analysis of nicotine-like receptor-ligand interactions in rodent brain homogenate, *J Neurochem* 1985;45:24-31. *See* AR (Vol. 141 Ref. 1684).

Larsson C, Lundberg PA, Halen A, *et al.*, In vitro binding of 3H-acetylcholine to nicotinic receptors in rodent and human brain, *J Neural Transm* 1987;69:3-18. *See* AR (Vol. 137 Ref. 1586).

Larsson C, Nilsson L, Halen A, *et al.*, Subchronic treatment of rats with nicotine: effects on tolerance and on [3 H]acetylcholine and [3 H]nicotine binding in the brain, *Drug Alcohol Depend* 1986;17:37-45. *See* AR (Vol. 141 Ref. 1677).

Nisell M, Nomikos GG, Svensson TH, Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area, *Synapse* 1994;16:36-44. *See* AR (Vol. 276 Ref. 3870).

Nordberg A, Romanelli L, Sundwall A, *et al.*, Effect of acute and subchronic nicotine treatment on cortical acetylcholine release and on nicotinic receptors in rats and guinea-pigs, *British Journal of Pharmacology* 1989;98(1):71-78. *See* AR (Vol. 131 Ref. 1454).

Nordberg A, Wahlstrom G, Amelo U, *et al.*, Effect of long-term nicotine treatment on [3-H]nicotine binding sites in the rats brain, *Drug Alcohol Depend* 1985;16:9-17. *See* AR (Vol. 141 Ref. 1678).

Nordberg A, Bergh C, Effect of nicotine on passive avoidance behaviour and motoric activity in mice, *Acta Pharmacol Toxicol Copenh* 1985;56(4):337-341. *See* AR (Vol. 274 Ref. 3820).

Nordberg A, Sundwall A, Pharmacodynamic effects of nicotine and acetylcholine biosynthesis, in mouse brain, *Acta Pharmacol Toxicol Copenh* 1983;52(5):341-347. *See* AR (Vol. 133 Ref. 1503).

Nordberg A, Larsson C, Studies of muscarinic and nicotinic binding sites in brain, *Acta Physiol Scand Suppl* 1980;479:19-23. *See* AR (Vol. 137 Ref. 1590).

Piloni A, Enzell CR, Mentzanis N-H, *et al.*, Studies on the identification of tobacco alkaloids, their mammalian metabolites and related compounds by gas chromatography- -Mass Spectrometry, *Beitrage zur Tabakforschung* 1976;8(6):339-349. *See* AR (Vol. 96 Ref. 704).

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Furthermore, numerous studies of the pharmacological effects and chemistry of nicotine and the sites and mechanisms of nicotine receptors in the brain have been funded by the Smokeless Tobacco Research Council.[1012] The Smokeless Tobacco Research Council

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Schievelbein H, Absorption of Nicotine Under Various Conditions (an introductory review), presented at the Nicotine Workshop (Nov. 1974), *Beitrage zur Tabakforschung* 1976;8(5):196-202. *See* AR (Vol. 60 Ref. 254).

Schmiterlow CG, Hansson E, Andersson G, *et al.*, Distribution of Nicotine in the Central Nervous System. *Annals of the New York Academy of Sciences* 1967;142:2-14. *See* AR (Vol. 152 Ref. 1859).

Schmiterlow CG, Hansson E, Tissue distribution of C 14-nicotine, in Von Euler US (ed.), *Tobacco Alkaloids and Related Compounds* 1965:75-86, ed. Von Euler US. *See* AR (Vol. 60 Ref. 256).

Siegel RA, Andersson K, Fuxe K, *et al.*, Rapid and discrete changes in hypothalamic catecholamine nerve terminal systems induced by audiogenic stress, and their modulation by nicotine-relationship to neuroendocrine function, *Eur J Pharmacol* 1983;91:49-56. *See* AR (Vol. 60 Ref. 262).

Svensson TH, Engberg G, Effect of nicotine on single cell activity in the noradrenergic nucleus locus coeruleus, *Acta Physiol Scand Suppl* 1980;479:31-34. *See* AR (Vol. 422 Ref. 7124).

Szuts T, Olsson S, Lindquist NG, *et al.*, Long-term fate of [14C]nicotine in the mouse: retention in the bronchi, melanin-containing tissues and urinary bladder wall, *Toxicology* 1978;10(3):207-220. *See* AR (Vol. 131 Ref. 1458).

[1012] Anand R, and Lindstrom J, Chromosomal localization of seven neuronal nicotinic acetylcholine receptor subunit genes in humans, in *Report of the Council for Tobacco Research - USA, Inc. 1992*, at 101. *See* AR (Vol. 465 Ref. 7874).

Bencherif M, Lukas RJ, Cytochalasin modulation of nicotinic cholinergic receptor expression and muscarinic receptor function in human TE671/RD cells: a possible functional role of the cytoskeleton, *Journal of Neurochemistry* 1993;61(3):852-864. *See* AR (Vol. 141 Ref. 1683).

Brino LRG, Keyser KT, Lindstrom JM, *et al.*, Immunohistochemical localization of nicotinic acetylcholine receptor subunits in the mesencephalon and diencephalon of the chick (Gallus Gallus), *The Journal of Comparative Neurology* 1992;317:325-340. *See* AR (Vol. 131 Ref. 1453).

Cholerton S, McCracken NW, Idle JR, Sources of inter-individual variability in nicotine pharmacokinetics, in *Nicotine and Related Alkaloids: Absorption, Distribution, Metabolism, and Excretion*, eds. Gorrod JW, and Wahren J (1993), at 219-253. *See* AR (Vol. 47 Ref. 70).

Gerzanich V, Anand R, Lindstrom J, *Homomers of α8 and α7 subunits of nicotinic receptors exhibit similar* channel but contrasting binding site properties, *Molecular Pharmacology* 1994;45(2):212-220. *See* AR (Vol. 276 Ref. 3861).

Hsu YN, Amin J, Weiss D, *et al.*, Chronic nicotine exposure decreases the activation of α4β2 but not α3β2 neuronal nicotinic receptors expressed in *xenopus* oocytes, in *International Symposium on Nicotine: The*

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Effects of Nicotine on Biological Systems II, eds. Clarke PBS *et al.* (Montreal: Jul. 21-24, 1994). *See* AR (Vol. 135 Ref. 1529).

Keyser KT, Britto LRG, Schoepfer R, *et al.*, Three subtypes of α-bungarotoxin - sensitive nicotinic acetylcholine receptors are expressed in chick retina, *Journal of Neuroscience*, Feb. 1993;13(2):442-454. *See* AR (Vol. 126 Ref. 1343).

Marks R, Lindstrom J, Schroder H, Cellular and subcellular visualization of the β2 - subunit of the nicotinic acetylcholine receptor in the mouse cerebral cortex, in *International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II*, eds. Clarke, PBS, *et al.*, at session 1, 4 (Montreal: Jul. 21-24, 1994). *See* AR (Vol. 104 Ref. 952).

McFarland BJ, Seidler FJ, Slotkin TA, Inhibition of DNA synthesis in neonatal rat brain regions caused by acute nicotine administration, *Developmental Brain Research* 1991;58:223-229. *See* AR (Vol. 414 Ref. 6940).

McLane DE, Wu X, Schoepfer R, *et al.*, Identification of sequence segments forming the α-bungarotoxin binding sites on two nicotinic acetylcholine receptor α subunits from the avian brain, in *Report of the Council for Tobacco Research - USA, Inc. 1991*. *See* AR (Vol. 19 Ref. 195-22).

McLane DE, Wu X, Lindstrom JM, *et al.*, Epitope mapping of polyclonal and monoclonal antibodies against two α-bungarotoxin-binding α subunits from neuronal nicotinic receptors, in *Report of the Council for Tobacco Research - USA, Inc. 1992*. *See* AR (Vol. 19 Ref. 195-23).

Navarro HA, Seidler FJ, Schwartz RD, *et al.*, Prenatal exposure to nicotine impairs nervous system development at a dose which does not affect viability or growth, *Brain Research Bulletin* 1989;23:187-192. *See* AR (Vol. 137 Ref. 1585).

Nelson S, Shelton GD, Lei S, *et al.*, Epitope mapping of monoclonal antibodies to *torpedo* acetylcholine receptor γ subunits, which specifically recognize the ε subunit of mammalian muscle acetylcholine receptor, in *Report of the Council for Tobacco Research - USA, Inc. 1992*. *See* AR (Vol. 19 Ref. 195-23).

Seeman JI, Secor HV, Armstrong DW, *et al.*, Enantiomeric resolution and chiral recognition of racemic nicotine and nicotine analogues by β-cyclodextrin complexation. Structure-enantiomeric resolution relationships in host-guest interactions, *Analytical Chemistry* 1988;60:2120-2127. *See* AR (Vol. 275 Ref. 3836).

Slotkin TA, Cho H, Whitmore WL, Effects of prenatal nicotine exposure on neuronal development: selective actions on central and peripheral catecholaminergic pathways, *Brain Research Bulletin* 1987;18(5):601-611. *See* AR (Vol. 137 Ref. 1573).

Slotkin TA, Navarro HA, McCook EC, *et al.*, Fetal nicotine exposure produces postnatal up-regulation of adenylate cyclase activity in peripheral tissues, *Life Sciences* 1990;47:1561-1567. *See* AR (Vol. 276 Ref. 3865).

Slotkin TA, Lappi SE, Tayyeb MI, *et al.*, Chronic prenatal nicotine exposure sensitizes rat brain to acute postnatal nicotine challenge as assessed with ornithine decarboxylase, *Life Sciences* 1991;49(9):665-670. *See* AR (Vol. 137 Ref. 1580).

Slotkin TA, Developmental effects of nicotine, in *International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II*, eds. Clarke PBS, *et al.*, at session 4, S15 (Montreal: Jul. 21-24, 1994). *See* AR (Vol. 60 Ref. 264).

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was formed by the major smokeless tobacco manufacturers to fund scientific studies on behalf of the manufacturers. One such study recognized that nicotine is "*the major pharmacologically active component of tobacco.*"[1013]

2. The Smokeless Tobacco Manufacturers Manipulate Nicotine Deliveries from Smokeless Tobacco in a Manner That Promotes Tolerance and Addiction in Users

The evidence in the record also demonstrates that smokeless tobacco manufacturers manipulate the nicotine delivery of their products to produce graduated deliveries of nicotine that promote tolerance and addiction. Specifically, the evidence shows that the nicotine deliveries of smokeless tobacco are manipulated so that products intended for new users deliver low amounts of nicotine, while products intended for experienced users deliver far higher amounts of nicotine. This manipulation of nicotine delivery is accomplished primarily

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Slotkin TA, Lappi SE, Seidler FJ., Impact of fetal nicotine exposure on development of rat brain regions: critical sensitive periods or effects of withdrawal?, *Brain Research Bulletin* 1993;31:319-328. *See* AR (Vol. 137 Ref. 1571).

Wahlsten JL, Lindstrom JM, Conti-Tronconi BM, Amino acid residues within the sequence region α55-74 of torpedo nicotinic acetylcholine receptor interacting with antibodies to the main immunogenic region and with snake α-neurotoxins, in *Report of the Council for Tobacco Research - USA, Inc. 1993*, at 166-167. *See* AR (Vol. 465 Ref. 7873).

Wahlsten JL, Lindstrom JM, Ostlie N, *et al.*, Myasthenia gravis: effect on antibody binding of conservative substitutions of amino acid residues forming the main immunogenic region of the nicotinic acetylcholine receptor, in *Report of the Council for Tobacco Research - USA, Inc. 1993*, at 166. *See* AR (Vol. 465 Ref. 7873).

Yu CI, Morgan DG, Wecker L, Northern blot analysis demonstrates the presence of three different transcripts of neuronal nicotinic acetylcholine receptor α4 gene in rat brain, in *International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II*, eds. Clarke PBS, *et al.*, at session 2, P10 (Montreal: Jul. 21-24, 1994). *See* AR (Vol. 104 Ref. 952).

[1013] Cholerton S, McCracken NW, Idle JR, Sources of inter-individual variability in nicotine pharmacokinetics, in *Nicotine and Related Alkaloids: Absorption, Distribution, Metabolism, and Excretion*, eds. Gorrod JW, Wahren J (1993):219-253, at 219 (emphasis added). *See* AR (Vol. 47 Ref. 70).

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through the use of chemicals that alter the pH (acidity or alkalinity) of the tobacco. The effect is to promote tolerance and addiction in users.

The evidence of nicotine manipulation in smokeless tobacco in a manner that promotes tolerance in addiction in users is extensive. First, evidence shows that products intended for new users deliver less nicotine than products intended for experienced users. These graduated nicotine deliveries lead to increased tolerance and addiction because they allow new users to avoid adverse reactions to nicotine by beginning with low-nicotine products, while allowing experienced users to obtain sufficient nicotine to sustain their addiction by progressing to high-nicotine products.

Second, governmental data on smokeless tobacco use confirms that the graduated nicotine deliveries promote tolerance and addiction. These data show that since the advent of smokeless tobacco products with graduated nicotine deliveries, the number of children and adolescents who use and are addicted to smokeless tobacco has risen substantially.

Third, evidence from internal company documents and marketing campaigns of the nation's largest smokeless tobacco manufacturer, UST, shows the conscious manipulation of nicotine deliveries. UST deliberately relies on an explicit "graduation process" that introduces new users to low-nicotine delivery products while providing experienced users with higher-nicotine delivery products.

In combination with the evidence that the manufacturers understand the pharmacological effects and uses of nicotine, this evidence of nicotine manipulation to ~~produce~~ pharmacological effects in users demonstrates that the effects of nicotine in

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smokeless tobacco on the structure and function of the body are "intended" by the manufacturers.

a. Evidence of Graduated Nicotine Deliveries

Absorption of a drug through the buccal mucosa in the mouth into the bloodstream can be increased or decreased by adjusting the pH of the drug. Pharmaceutical companies regularly alter pH by adding alkaline or acidic additives to drugs to increase or decrease their absorption into the bloodstream. Raising the pH converts many drugs from an ionized form into a non-ionized or "free" form that more readily crosses biological membranes.[1014]

Nicotine absorption is affected in this manner by pH levels. Increasing the pH of nicotine converts ionized nicotine into non-ionized nicotine, rendering it significantly more absorbable in the mouth.[1015] For this reason, the manufacturer of nicotine gum adds sodium carbonate to increase pH and enhance the absorption of nicotine.[1016] Tobacco industry-supported researchers have acknowledged that nicotine absorption in the mouth increases as a function of pH and that "the pharmacological response is clearly dependent on the amount of nicotine in the mouth as free base."[1017] Indeed, the senior vice president for marketing at

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[1014] Benet LZ, Steiner LB, *Pharmacokinetics: The dynamics of drug absorption, distribution, and elimination* in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (1990), 3-32, at 4-5. *See* AR (Vol. 711 Ref. 14).

[1015] Surgeon General's Report, 1988, at 29. *See* AR (Vol. 129 Ref. 1592).

[1016] Henningfield JE, Radzius A, Cooper TM, *et al.*, Drinking coffee and carbonated beverages blocks absorption of nicotine from nicotine polacrilex gum. *Journal of the American Medical Association*, 1990;264:1560-1564. *See* AR (Vol. 29 Ref. 491-2).

[1017] Armitage AK, Turner DM, Absorption of nicotine in cigarette and cigar smoke through the oral mucosa, *Nature*, 1970;226:1231-1232, at 1232. *See* AR (Vol. 143 Ref. 1810).

Cholerton S, McCracken NW, Idle JR, Sources of inter-individual variability in nicotine pharmacokinetics, in *Nicotine and Related Alkaloids: Absorption, Distribution, Metabolism, and Excretion*, eds. Gorrod JW, Wahren J (1993), at 220-221 ("Absorption of nicotine from chewing tobacco and nicotine gum is facilitated by buffering of the preparations to an alkaline pH (approx. 8.5)"). *See* AR (Vol. 47 Ref. 70).

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UST conceded that it was his understanding that "if the pH of the snuff product is raised, . . . the rate of absorption of the nicotine would be increased in the user's mouth."[1018]

The data collected and analyzed by FDA[1019] and others[1020] demonstrate that moist snuff products marketed as "starter" products have relatively low pH levels, while products for established users have significantly higher pH levels, resulting in a pattern of graduated delivery of free nicotine. UST's principal line of starter products is its "Skoal Bandits" line. The pH levels for Skoal Bandits are low, ranging from 5.2 to 5.6 for Skoal Bandits Classic to 6.8 to 7.1 for Skoal Bandits Mint; the free nicotine provided by Skoal Bandits is also low, ranging from 0.2% to 0.4% for Skoal Bandits Classic to only 6.4% to 9.9% for Skoal Bandits Mint. *See* Jurisdictional Analysis, 60 FR 41737. Likewise, another UST starter product, "Happy Days," has a pH of 6.0 and provides only 0.9% free nicotine. In contrast, UST's principal product for established users, Copenhagen, has a pH of 7.7 to 8.1. Because pH is measured on a logarithmic scale, the alkalinity of Copenhagen is approximately two

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[1018] The exchange from the *Marsee* trial transcript on this point was:

> Q: And correspondingly, if the pH of the snuff product is raised, then, the rate of absorption of the nicotine from the snuff product would be increased in the user's mouth?
> A: Although I am not an expert on this, that is to the best of my understanding correct.

Deposition of Erik Lindqvist, *Marsee v. U.S. Tobacco*, Civil Action No. 84-2777R (W.R. Ok. 1986). Transcript of jury trial proceedings, at 1668. *See* AR (Vol. 29 Ref. 489-2). The relationship between ionized nicotine and nicotine in its free form is thus similar to the relationship between cocaine and "free-base" or "crack" cocaine. Increasing the pH of cocaine, through the addition of alkaline additives such as sodium bicarbonate and ammonia, converts cocaine salt into free-base or crack cocaine, thereby significantly increasing the rate at which the cocaine is absorbed into the bloodstream. Siegel RK, Part III cocaine free base use, *Journal of Psychoactive Drugs* 1982;14:311-318, 352-359. *See* AR (Vol. 711 Ref. 23).

[1019] The table on the next page presents the results of the analyses performed by the two FDA laboratories in St. Louis, Missouri, and Cincinnati, Ohio.

[1020] Djordjevic MV, Hoffmann D, Glynn T, *et al.*, US commercial brands of moist snuff, 1994. Assessment of nicotine, moisture, and pH. *Tobacco Control*, 1995;4:62-66. *See* AR (Vol. 528 Ref. 97, appendix 9).

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II.D.2.

TOTAL NICOTINE

MANUFACTURER/ PRODUCT NAME	pH		%Free Nicotine*		Content(mg/gm)**	
	St.Louis	Cinc.	St.Louis	Cinc.	St.Louis	Cinc.
U.S. Tobacco Co.						
Skoal Key	-	8.22	-	61.3	-	12.4
Copenhagen Snuff	8.14	7.71	56.5	32.7	13.2	13.8
Skoal L.C. Class	8.04	7.92	51.1	44.5	12.7	13.8
Skoal L.C. Wint.	7.50	7.57	23.1	26.0	12.7	13.9
Skoal L.C. Mint	7.35	7.52	17.6	24.0	13.2	13.7
Skoal L.C. Spear.	7.20	7.50	14.0	23.3	12.5	13.8
Skoal Or.F.C. Wint.	-	7.41	-	19.7	-	13.6
Skoal L.C. Strai.	7.47	7.41	22.0	19.5	12.1	13.8
Skoal L.C. Cherry	7.15	7.38	12.3	18.5	12.5	13.6
Skoal Band. Mint	6.83	7.06	6.4	9.9	6.7	8.8
Skoal Band. Wint.	6.56	6.72	3.3	4.8	7.8	8.2
Happy Days L.C. Mint	6.00	-	0.9	-	13.9	
Skoal Band. Strai.	-	5.48	-	0.3	-	10.8
Skoal Band. Class.	5.61	5.23	0.39	0.2	10.4	9.9
Helme Tobacco Co.* **						
Redwood Full Flavor	-	7.52	-	24.0	-	12.6
Silver Cr. L.C.	-	7.22	-	13.7	-	6.0
Cooper Wint. L.C.	-	6.99	-	8.5	-	5.7
Gold River L.C.	-	5.77	-	0.6	-	6.4
Conwood Co.						
Kodiak Wint.	8.20	8.22	59.9	61.0	11.4	11.7
Kodiak Choice Wint.	-	7.98	-	47.7	-	11.4
Kodiak Straight	7.39	7.82	19.0	38.4	10.6	10.4
Hawken Wint.	5.56	5.58	0.35	0.4	4.4	0.4
Pinkerton Tobacco Co.						
Redman F.C. Ex. Wint.	-	7.58	-	-	-	12.3
Renegade Wint.	6.81	7.17	5.8	-	13.2	11.8

L.C. = long cut

* Calculated using the Henderson-Hasselbach Equation for acid base equilibrium. This calculation strictly is dependent on the pH determination. Any error in the pH determination will affect the percent free nicotine calculation.

** Measured on wet basis

*** Now Swisher International, Inc.

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orders of magnitude higher than the alkalinity of Skoal Bandits Classic and Happy Days (as measured in hydrogen ion concentrations). The level of free nicotine provided by Copenhagen is 33% to 57%, also far higher than the levels provided by Skoal Bandits or Happy Days.[1021]

The same pattern of graduated nicotine deliveries is found in the smokeless tobacco products of other manufacturers. Conwood's principal line of moist snuff starter products, "Hawken," has a pH of 5.6 and provides 0.4% free nicotine, whereas Conwood's product marketed for established users, "Kodiak-Wintergreen," has a pH of 8.2 and provides about 60% free nicotine.[1022] Similarly, the principal starter product of Swisher International, Inc. (formerly Helme Tobacco Co.), "Gold River L.C.," has a pH of 5.8 and provides 0.6% free nicotine, whereas its product marketed for established users, "Redwood Full Flavor," has a pH of 7.5 and provides 24% free nicotine.[1023]

These graduated nicotine deliveries directly promote tolerance and addiction. New users of smokeless tobacco have not developed a tolerance to nicotine. As a result, as a UST study documented, too much nicotine causes adverse reactions such as nausea and vomiting in new users,[1024] discouraging future experimentation with smokeless tobacco. Once tolerance to nicotine is developed, however, increasing doses of nicotine are required to

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[1021] *See* Table of "Total Nicotine" above.

[1022] *Id.*

[1023] *Id.*

[1024] U.S. Tobacco Company, Pharmacokinetics of Nicotine and Its Major Metabolites in Naive and Habituated Snuff Takers, Plaintiff's exhibit 3.27 from *Marsee v. U.S. Tobacco*, Civil Action No. 84-2777R (W.D. Ok. 1986), at 9. *See* AR (Vol. 24 Ref. 317).

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produce the desired pharmacological effects.[1025] Thus, if nicotine levels were kept uniformly low to accommodate new users, the experienced user would not obtain the higher level of nicotine delivery needed to satisfy the user's addiction and to provide other desired pharmacological effects.

Graduating nicotine deliveries avoid these consequences and lead to increased tolerance and addiction. The low levels of nicotine delivery in starter brands, such as Skoal Bandits, allow the new user to develop a tolerance to nicotine[1026] without nausea and other adverse reactions. Once this tolerance is developed, the high levels of nicotine delivery in brands such as Copenhagen provide the experienced user with the desired increase in nicotine dose. Nicotine addiction is the final result.

There are several techniques the smokeless manufacturers use to achieve control over pH levels in smokeless tobacco. According to one report, pH adjustment is "done through fermentation, by adding alkaline buffering agents such as sodium carbonate and ammonium carbonate, or by altering the moisture content."[1027] The Swedish Tobacco Company, which like Pinkerton Tobacco Company is owned by Procordia AB, has admitted that "*[i]n order to release the nicotine from the tobacco, the snuff is made slightly alkaline—sodium carbonate is added. . . .*"[1028] The Smokeless Tobacco Council has also reported that two alkaline

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[1025] Surgeon General's Report, 1988, at 44-45. *See* AR (Vol. 129 Ref. 1592).

[1026] Connolly GN, Orleans CT, Blum A, Snuffing tobacco out of sport, *American Journal of Public Health* Mar. 1992;82(3):352. *See* AR (Vol. 94 Ref. 629).

[1027] Connolly GN, Marketing of Nicotine Addiction By One Oral Snuff Manufacturer, *Tobacco Control* 1995;4:73-79, at 74. *See* AR (Vol. 528 Ref. 97, appendix 9).

[1028] Swedish Tobacco Company, Smokeless Tobacco from Gothenburg, 1994, appendix B, quoted in statement of Gregory N. Connolly in *Health Effects of Smokeless Tobacco: Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 53 (Nov. 29, 1994) (emphasis added). *See* AR (Vol. 710 Ref. 4).

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